APPROACHES TO THE SYNTHESIS OF EUPAROTIN

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

by

Gerard L. Hasenhuettl

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

April, 1977

APPROACHES TO THE

SYNTHESIS OF EUPAROTIN

Approved:

Drury S. Caine, III., Chairman

Herbert O. House

Leon H. Zalkow

Date approved by Chairman: April 4, 1977

ACKNOWLEDGMENTS

The author would like to express his appreciation to Dr. Herbert O. House and Dr. Leon Zalkow for their helpful comments and for reading this manuscript. A note of thanks is also in order for Dr. F. Norman Tuller and Dr. Paul Ingwalson for their suggestions and to Mr. Lawrence Abbey for obtaining the mass spectra in this work. A very special indebtedness is expressed to Dr. Drury S. Caine whose patient guidance made the failures of this work a little less depressing and the successes much more rewarding.

Gratitude must also be expressed to Dr. J. C. Lester whose surgical skills allowed the author to resume a normal career. A profound appreciation is expressed to Julie and Heather Hasenhuettl, for without their love and encouragement this work could never have been undertaken.

TABLE OF CONTENTS

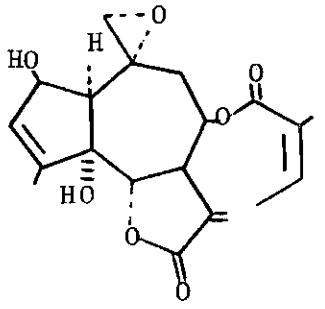
TABLE OF CONTENTS (Concluded)

GLOSSARY OF ABBREVIATIONS

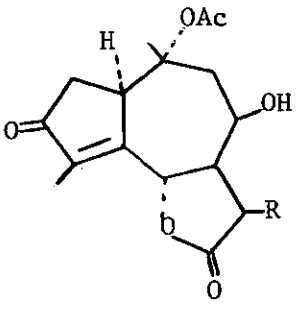
Anal.	C,H analysis
b.p.	boiling point
cm^{-1}	wave numbers (ir spectrum)
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
eV	electron volt
GLC	gas-liquid chromatography
Hz	Hertz (cycles per second, nmr spectrum)
ir	infrared
J	coupling constant (mass spectrum)
LAH	lithium aluminum hydride
mm	millimeters of mercury (pressure)
m/e	mass to charge ratio (nmr spectrum)
m.p.	melting point
nm	nanometers (millimicrons, uv spectrum)
nmr	nuclear magnetic resonance
ppm	parts per million (nmr spectrum)
PTSA	p-toluenesulfonic acid
THF	tetrahydrofuran
TMS	tetramethylsilane
UV	ultraviolet
ε	extinction coefficient (uv spectrum)
λ	wavelength

SUMMARY

In an investigation of possible synthetic routes to the naturally occurring sesquiterpene lactone euparotin (1), a synthesis of intermediate 21 was proposed.



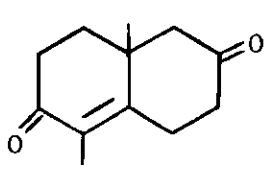
1



21

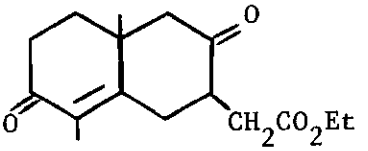
R = CH_3 or H

Starting with known racemic diketone 32, enone lactone 46 was prepared by enamine alkylation and subsequent reduction with potassium tri-sec-butylborohydride.



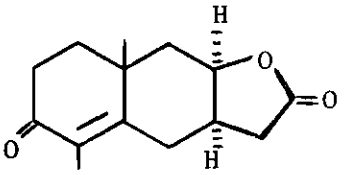
32

1) pyrollidine, benzene
2) ethyl bromoacetate



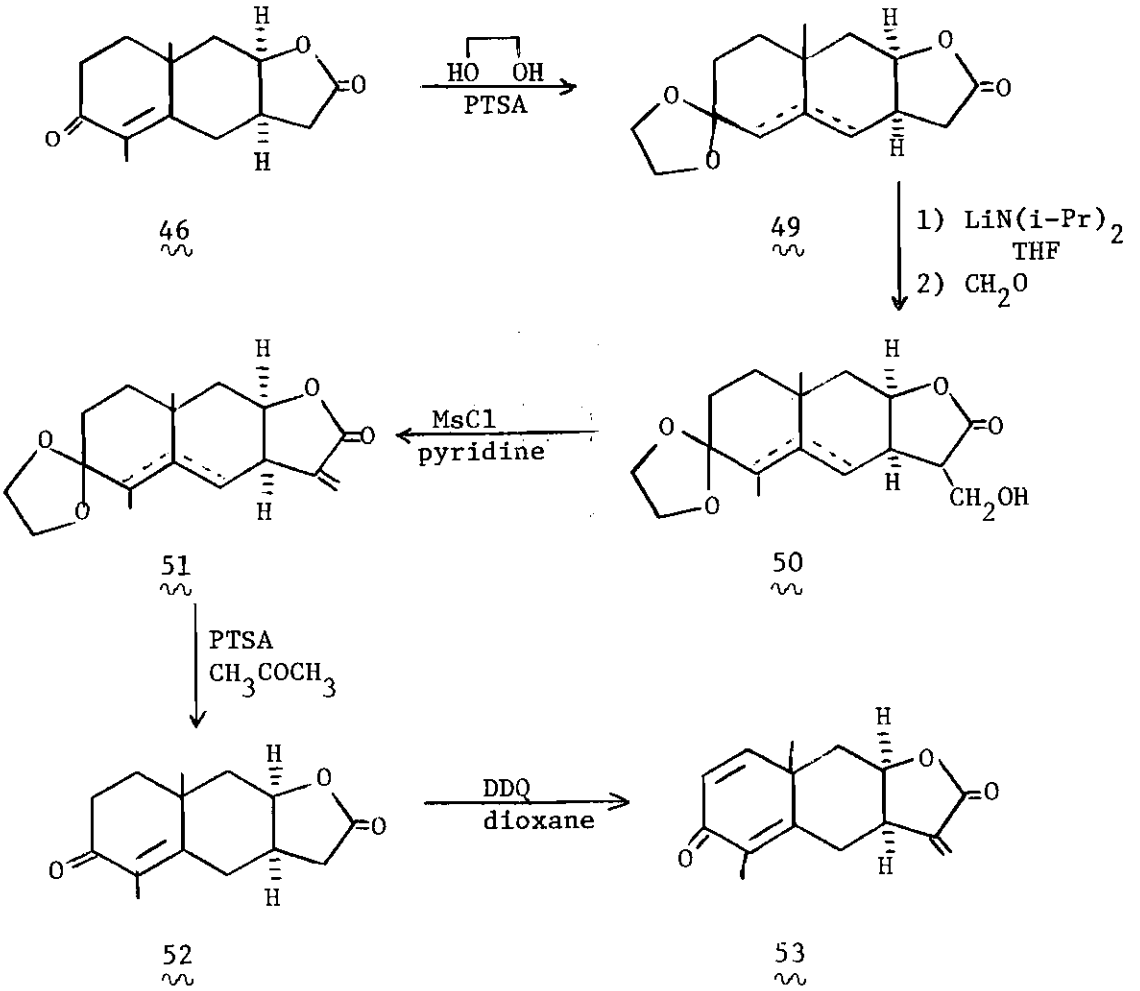
45

K (s-Bu)$_3$BH, THF



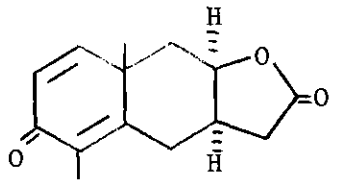
46

From the enone lactone 46 a successful synthesis of (+)-yomogin (53) was accomplished. Ketalization with ethylene glycol gave the relatively unstable ketal lactone 49. Enolate formation and addition of gaseous formaldehyde gave hydroxymethyl compound 50 which was subsequently dehydrated to α-methylene lactone 51. The synthesis was completed by deketalization to 52 and dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone to produce (+)-yomogin (53).

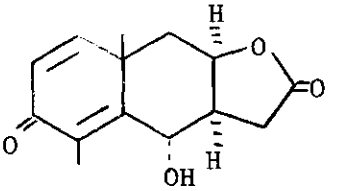


46 49 50 51 52 53

Oxidation of 46 with DDQ produced dienone lactone 56 in 35% yield. Subsequent efforts at hydroxylation with selenium dioxide in an attempt to produce C-8 hydroxylated compound 57 were unsuccessful.

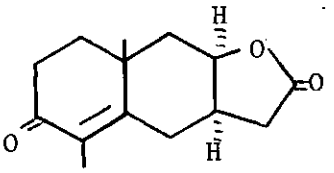


56



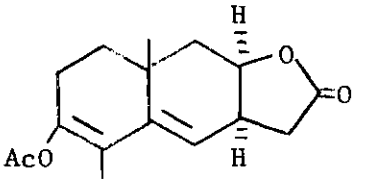
57

Enone lactone 46 was reacted with acetic anhydride and sulfuric acid to produce enol acetate in 45% yield. However, subsequent attempts at epoxidation and hydrolysis to produce 57 also were unsuccessful.



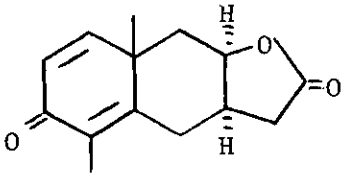
46

Ac_2O, H_2SO_4

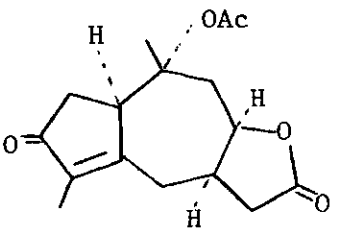


58

Photolysis of dienone lactone 56 in glacial acetic acid produced photoproduct 60 in 50% yield. A subsequent attempt at allylic hydroxylation of 60 was unsuccessful.



56



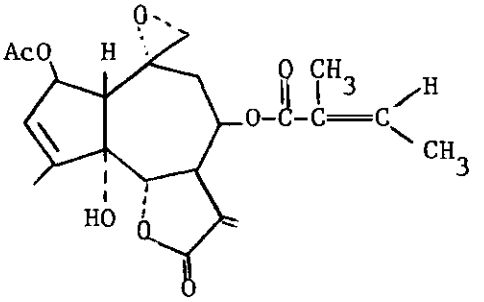
60

Although a synthesis of intermediate 21 has been unsuccessful, photoproduct 60 has been produced which incorporates four of the desired unsymmetrical centers present in euparotin (1). A total synthesis of racemic yomogin has been realized and yomogin itself may prove a useful intermediate for the synthesis of the more complex guaianolide 1.

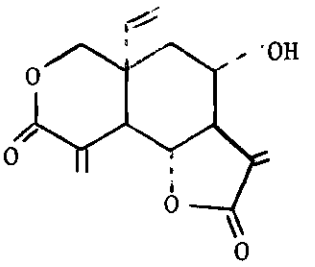
CHAPTER I

INTRODUCTION

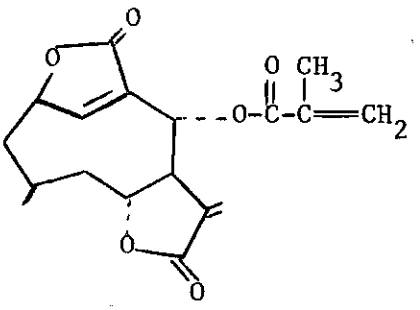
Several sesquiterpene lactones have been observed to have potent antitumor properties. The functionality responsible for this activity appears to be an α-methylene lactone.[1] Some of the most active naturally occurring compounds are euparotin acetate 1, vernolepin 2, and elephantopin 3.



1



2

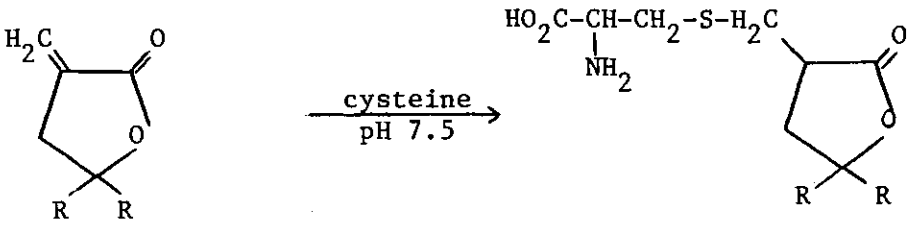


3

Although compounds containing only the α-methylene function show antitumor properties, a major enhancement effect is observed for oxygen substituents which are homoallylic to the α-methylene group.[2]

A total synthesis of a compound such as euparotin from readily available starting materials would not only provide a more convenient source of the active compound, but might also lead to intermediates that might possibly be active. Such intermediates might provide evidence for the structural requirements and stereochemistry necessary for anti-tumor activity in the guaianolide series.

The biochemical mode of action of these α-methylene lactones is thought to involve the Michael addition of a sulfhydryl group. This is illustrated for cysteine in Scheme 1.

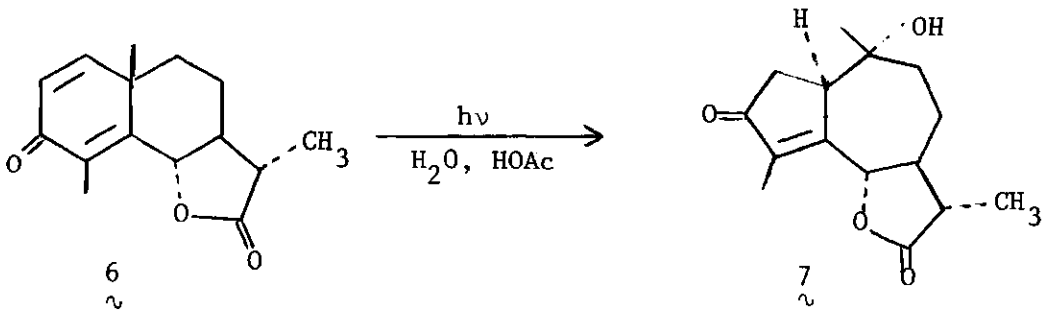


4 ≈ 5 ≈

Scheme 1.

The appreciable toxicity of these compounds is thought to result from non-specific reaction with metabolically essential intracellular proteins.

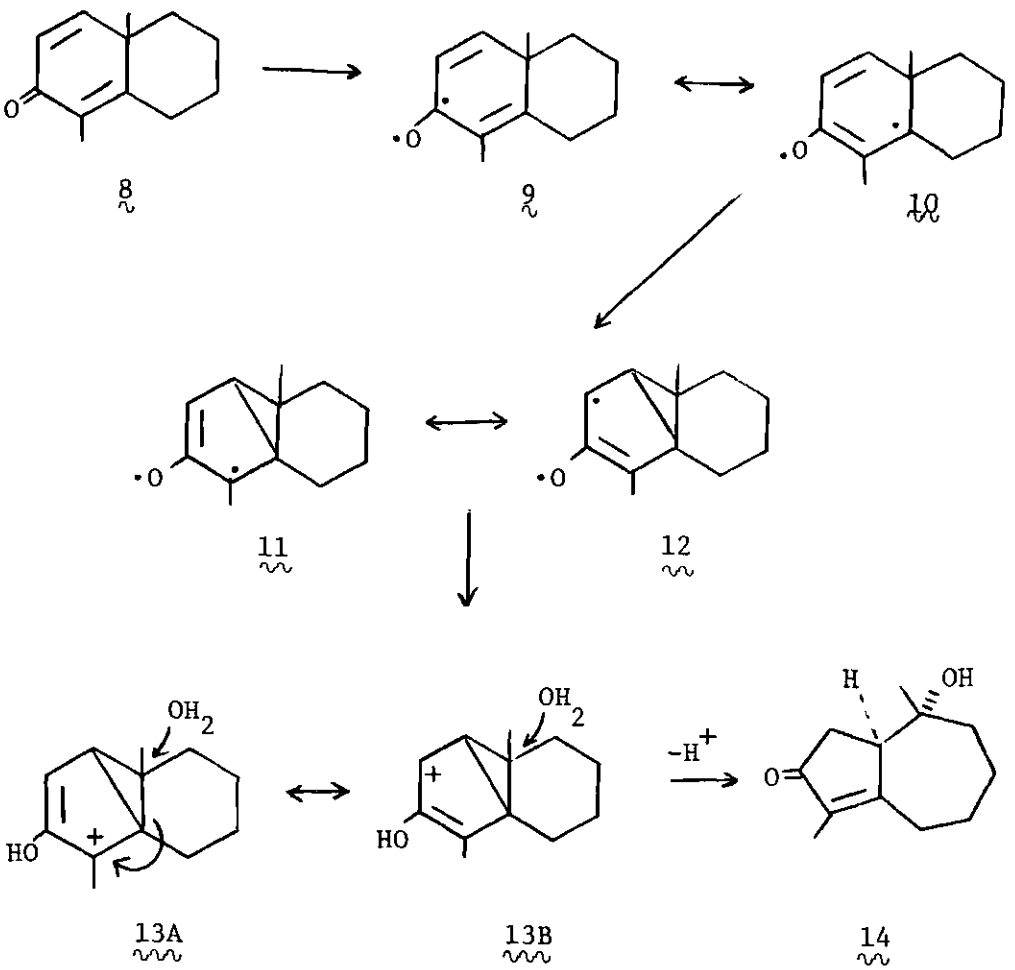
An attractive synthetic route to euparotin is suggested by the stereospecific photochemical rearrangement observed for α-santonin by Barton[3] (Scheme 2).



6 7

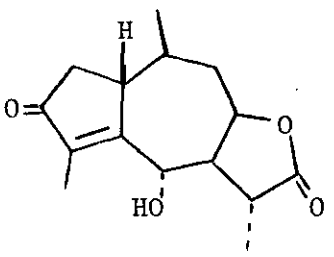
Scheme 2.

A mechanism for this rearrangement was proposed by Zimmerman[4] which is illustrated in Scheme 3 using a model bicyclic dienone. The process shown appears to occur in four steps: 1) $n \rightarrow \pi^*$ excitation to a diradical represented by 9 and 10, 2) bond reorganization resulting in 1,5-bonding to form a diradical represented by 11 and 12, 3) $\pi^* \rightarrow n$ electron demotion with concomitent protonation to carbonium ion 13A and 13B, and 4) solvolytic attack at C-10 to produce the 5/7-fused product 14. Cleavage of the alternative bond of the cyclopropane ring in 13 may also occur in certain cases depending upon the presence and location of substituents.

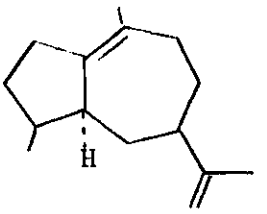


Scheme 3.

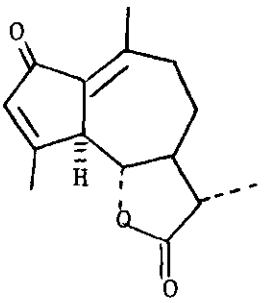
The stereospecificity of this reaction has been used to advantage in the synthesis of several naturally occurring compounds. Some of these compounds are geigerin 15[5], α-bulnesene 16[6], deacetoxymatricarin 17[7], and cyclocolorenone 18[8].



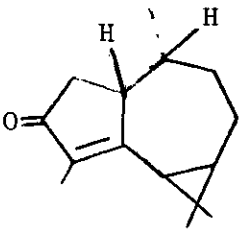
15



16

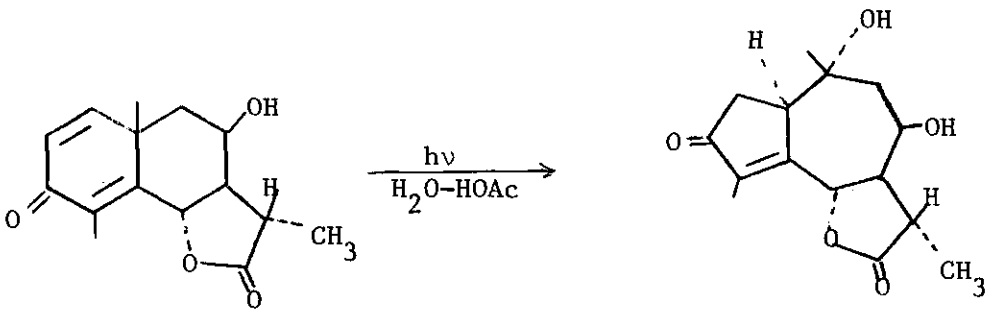


17



18

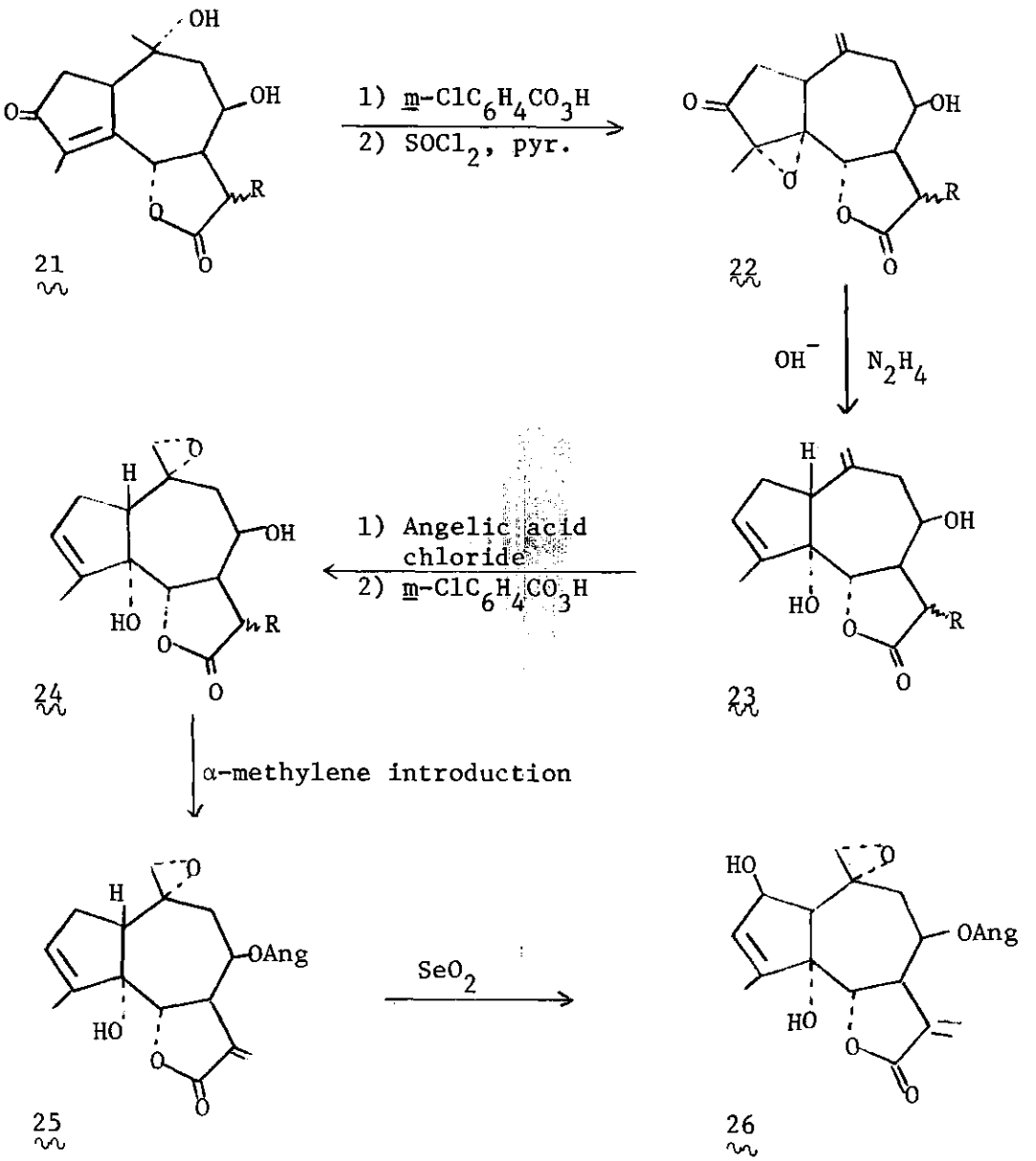
8-Epi-artemisin 19 has been photolyzed by Barton et al.[9] (Scheme 4) to give the 5/7-fused compound 20. It would seem that 20 would be an attractive intermediate for the synthesis of euparotin.



19 20

Scheme 4.

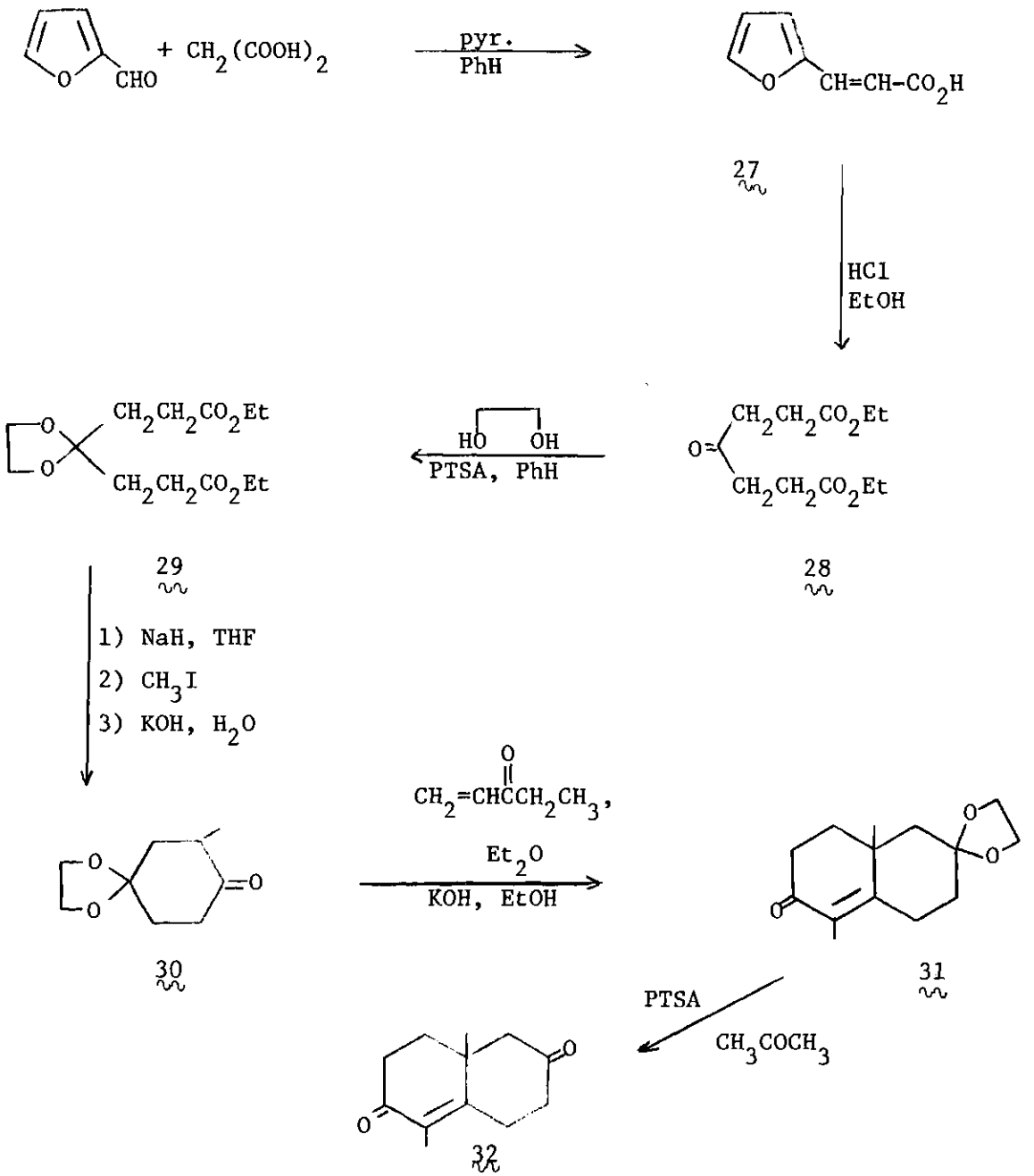
Since artemisin is prohibitively expensive ($21.00/10 mg, K & K Laboratories) as a starting material, a total synthesis of this type intermediate was considered to be a viable alternative. If intermediates of the type 20 or 21 (R = H) were available, the synthesis might be completed as illustrated in Scheme 5.



Scheme 5.

Epoxidation of the molecule 21 should give the 4α,5α-epoxide because of the appreciable steric hindrance of the C-10 methyl group on the β side of the molecule. Kinetically controlled dehydration should then result in the exomethylene group. Wharton has described the reaction of α,β-epoxy ketones with hydrazine and by analogy, 22 should be readily convertible to 23.[10] The secondary alcohol of 23 should be selectively acylated by the acid chloride of angelic acid. Selective epoxidation with m-chloroperbenzoic acid should proceed preferentially from the α-side due to the presence of the C-5 α-hydroxy function.[11] A myriad of methods has recently become available for the introduction of the α-methylene moiety on the lactone ring.[12] The method of Grieco and Hiroi uses lithium diisopropylamide to form the enolate, hydroxymethylation with gaseous formaldehyde, and elimination to form the α-methylene lactone. Potentially this could be used in this synthetic sequence if 21 (R = H) were the starting material. If compound 20 were employed as the starting material one of several procedures for converting α-methly-γ-lactones to α-methylene-γ-lactones could be employed.[12] Selenium dioxide allylic hydroxylation should give racemic euparotin 26.

The objective of this study was to synthesize intermediates of type 20 or 21 (R = H) starting with the known[13] diketone 32. A synthesis of this diketone is illustrated in Scheme 6.



Scheme 6.

Elaboration of the B ring to incorporate the lactone and hydroxyl function, followed by oxidation of the A ring to the dienone should give the desired intermediate.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Solvent removal under reduced pressure was carried out using a Buchi Rotavapor rotary evaporator. Thin layer chromatography was carried out on Eastman Chromagram sheets coated with silica gel or on Analtech Uniplate precoated silica gel G plates. Column chromatography was carried out using Grace grade 923, 100-200 mesh silica gel; EM neutral aluminum oxide 90; or Fisher 100-200 mesh florisil in the ratio of 25 g of absorbent per gram of mixture.

Nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian Model A-60D or T-60 spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane which was used as an internal standard. The abbreviations s, d, t, q, and m refer, respectively, to singlet, doublet, triplet, quartet, and multiplet, and coupling constants (J) are reported in Hz. Infrared spectra were recorded using a Perkin-Elmer Model 457 spectrophotometer and absorptions are reported in cm^{-1}. For spectra obtained in solutions, 0.1 mm sodium chloride cells were used. Ultraviolet spectra were obtained on a Beckman Model DB-GT recording spectrophotometer using one centimeter matched quartz cells and 95% ethanol as the solvent. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7 or a Varian Model M-66 spectrometer with a 70 electron volt source. Gas chromatographic analyses were obtained using a Perkin-Elmer Model 881 flame ionization gas chromatograph. The following columns were used: A(6 ft x 0.125 in, 10% SE-30 on Chromosorb W):

B(6 ft x 0.125 in, 10% Carbowax K-20M on Chromosorb W). Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are also uncorrected. Carbon and hydrogen analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

CHAPTER III

EXPERIMENTAL 12

β-Furylacrylic Acid (27)[14]

Malonic acid (630 g, 6.05 mol), 20 ml morpholine, 600 ml pyridine, and 2700 ml benzene were placed in a 5-l.three-necked flask equipped with a dropping funnel, mechanical stirrer, a Dean-Stark trap and a condenser. The mixture was heated to reflux and freshly distilled furfural (575 g, 6.0 mol) was added dropwise with stirring over a 1.5 hr period. After addition was complete, the solution was stirred for 4 hr while 102 ml water was collected in the Dean-Stark trap. The amber mixture was then cooled to room temperature and extracted with five 400-ml portions of 6 N aqueous ammonium hydroxide solution. The basic solution was cooled in an ice bath and acidified with cold 6 N aqueous hydrochloric acid until precipitation appeared to be complete. The mixture was filtered and then washed with cold water until the filtrate was light yellow. Drying of the solid in air for 48 hr yielded 710 g (85%) of β-furylacrylic acid m.p. 126-129°. A small amount of the material was recrystallized from ethanol-water to give white crystals: m.p. 138-140° (lit.[14] 139-140°).

Diethyl-γ-oxopimelate (27)[15]

β-Furylacrylic acid (247 g, 1.8 mol) and 2 l. of 95% ethanol were placed in a 3-l. three-necked flask fitted with a condenser, mechanical stirrer, and a gas inlet tube. Gaseous hydrogen chloride was

bubbled into the stirred solution at a rapid rate to cause the solution to reflux. Passage of the gas was maintained for 2 hr. Heat was applied and the mixture refluxed for an additional 4 hr. The mixture was then cooled, the volume was reduced to approximately 1000 ml by distillation under reduced pressure, and the solution extracted with 2000 ml benzene. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution until the aqueous phase was alkaline to pH paper. To facilitate separation of the phases, 100 ml of a saturated aqueous NaCl solution was added with each washing. The organic phase was then washed with 200 ml water. The benzene solution was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Distillation of the residue gave 303 g (73%) of diethyl-γ-oxopimelate: b.p. 120-123° (1 mm) (lit.[15] 160-164° (6 mm)); ir ($CHCL_3$) 1718 cm^{-1}; nmr δ (CCL_4) 4.10 (q, J = 7.0 Hz, 4H), 2.55 (br. m, 8H), and 1.22 ppm (t, J = 7.0 Hz, 6H).

Diethyl γ, γ-ethylenedioxypimelate (29)[16]

Diethyl-γ-oxopimelate (101 g, 0.44 mol), 250 ml benzene, 0.2 g PTSA acid, and 31 ml ethylene glycol were introduced into a 1-l. round-bottom flask equipped with a magnetic stirrer and a Dean-Stark trap fitted with a condenser. The solution was heated to reflux and stirred for 16 hr while 7.5 ml of water was collected in the Dean-Stark trap. The solution was washed with three 50-ml portions 5% aqueous $NaHCO_3$ solution followed by a 50-ml portion 10% aqueous NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. GLC analysis (column A, 100-200° @ 12°/min.) showed peaks at retention times of 9 min (keto diester) and 11.5 min (ketal diester). The residue was distilled through an 18"-column

packed with glass helices and five fractions, which showed the indicated ketone/ketal ratios on GLC were collected: 1) b.p. 70-92° (1 mm), 35:1; 2) b.p. 96-127° (1 mm), 25:1; 3) 127-131° (1 mm), 1:1; 4) 132-136° (1mm), 1:70; 5) 133-139° (1 mm), 1:99 (lit. 140-145° (0.5 mm)[13]). Fractions 4 and 5 were combined to give 92 g (83%) of 18: ir ($CHCl_3$) 1733 cm^{-1}; nmr δ (CCl_4) 4.05 (q, J = 7.0 Hz, 4H), 3.89 (s, 4H), 2.2 (m, 8H, and 1.24 ppm (t, J = 7.0 Hz, 6H).

2-Methyl-4-ethylenedioxycyclohexanone (30)

Sodium hydride (59.5 g of a 50% dispersion in mineral oil, 1.24 mol) was placed in a 5-l. three-necked flask equipped with a mechanical sitrrer, a dropping funnel and condenser. Three 200-ml portions of hexane were introduced, sitrred, and the resulting solution was withdrawn by a long needle attached to a syringe in order to remove the mineral oil. THF (2 l.) was distilled directly into the reaction flask from 5 g $LiAlH_4$, 0.5 ml of absolute ethanol was added and diethyl-γ, γ-ethylenedioxypimelate (340 g, 1.24 mol) was added dropwise with stirring. If the reaction had not started (as evidenced by vigorous evolution of hydrogen) by the time one-third of the ketal diester had been added, the addition was stopped and the mixture heated at reflux for 1-2 hr to initiate the reaction. The reaction mixture was then cooled to room temperature and the addition of the ketal diester was continued. After addition was complete, the mixture was stirred at room temperature for 12 hr and then at reflux for 30 min. The mixture was then cooled to 0° in an ice-salt bath and 213 g (1.5 mol) methyl iodide was added dropwise with stirring. The mixture was then stirred at room temperature for 36 hr. The solvent was removed under

reduced pressure and the residue partitioned between 2000 ml benzene and 500 ml water. The phases were separated and the organic phase was washed with three 200-ml portions of 1 N aqueous NaOH solution and one 200-ml portion of 10% aqueous NaCl solution. The benzene was removed under reduced pressure and the residue heated at reflux with 1500 ml 1 N KOH solution for 48 hr. The organic phase was separated and the aqueous phase was extracted with three 100-ml portions of benzene. The organic phases were combined and dried over $MgSO_4$, filtered, and the benzene removed under reduced pressure. The residue was distilled to give 104 g (44%) of 2-methyl-4-ethylenedioxycyclohexanone, b.p. 68-70° (0.5 mm) (lit.[16] 98-100° (4 mm), which exhibited a single peak on GLC analysis (column A, 100-200° @ 12°/min) with a retention time of 8.7 min. The product exhibited the following spectral properties: ir ($CHCl_3$) 1718 cm^{-1}; nmr δ (CCl_4) 3.99 (s, 4H) 2.1 (br. m., 7H) and 0.99 ppm (d, J = 7.8 Hz, 3H).

Ethyl Vinyl Ketone[17a]

Aluminum chloride (355 g, 2.7 mol) and 450 ml dry 1,2-dichloroethane (freshly distilled from P_2O_5) were placed in a 1000-ml three-necked flask equipped with a thermometer, gas inlet tube, mechanical stirrer, and a condenser. Propionyl chloride (245 g, 2.66 mol) was added to the mixture in a slow stream with stirring. The reaction mixture was cooled to 0-5° in an ice-salt bath and maintained at that temperature while dry ethylene was passed through the mixture for 6 hr. The mixture was poured over a slush of ice mixed with 500 ml conc. HCl while the temperature was kept below 20°. The organic phase was separated and washed with three 100-ml portions of 10% HCl and one 100-ml portion of

water. The solution was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 204 g (64%) of 1-chloro-3-pentanone which was used without purification.[17b]

In a 200-ml flask equipped with a variable take-off distilling head and addition funnel was placed sodium benzoate (400 g, 2.7 mol) and 1000 ml water. The mixture was heated to reflux and 200 g of the 1-chloro-3-pentanone was added over a 30 min period. When the vapor temperature dropped to approximately 85°, the variable take-off head was set for distillation and steam distillation was carried out until the temperature reached 99°. The organic phase of the distillate was separated and dried over anhydrous $CaCl_2$. The yield of crude product was 80 g (54%). The material was redistilled immediately before use b.p. 48-50° (95 mm) (lit. 44-45° (95 mm)[17a]); ir 1672 and 1620 cm^{-1}.

6, 6-Ethylenedioxy-1,10 β-dimethyl-$\Delta^{1,9}$-octal-2-one (31)[18]

A solution of KOH (22.5 g, 0.40 mol) in 75 ml absolute ethanol was placed in a 1000-ml three-necked flask equipped with a magnetic stirrer, addition funnel, nitrogen inlet, and a thermometer. Diethyl ether (300 ml) was added and the mixture cooled to 0-5° in an ice-salt bath. 2-Methyl-4-ethylenedioxycyclohexanone (85 g, 0.50 mol) was added dropwise over a 15 min period and the solution was stirred for 45 min. A solution of ethyl vinyl ketone (33.6 g, 0.40 mol) in 250 ml diethyl ether was added dropwise over a 1 hr period under a nitrogen atmosphere while the temperature was maintained at 0-5°. The reaction mixture was allowed to warm to room temperature, stirred for 1 hr, poured over 1000 g of ice, and the layers were separated. The aqueous layer was extracted with three 100-ml portions of diethyl ether. The combined

organic layers were dried over anhydrous Na_2SO_4, filtered, and the ether was removed under reduced pressure. Distillation of the residue gave a forerun, b.p. 68-70° (0.5 mm), of starting material followed by 61 g (65%) of 31: b.p. 136-138° (0.25 mm) lit.[18] 140-142° (0.3 mm). GLC analysis (column A, 100-200° @ 12°/min) of the product showed that it contained a single component with a retention time of 10.8 min. The product also showed: ir ($CHCl_3$) 1653 and 1210 cm^{-1}; nmr δ (CCl_4) 4.10 (s, 4H), 2.7 (m, 2H), 2.4 (br. m, 8H), 1.80 (s, 3H), and 1.32 ppm (s, 3H).

1,10β-Dimethyl-$\Delta^{1,9}$-octalin-2,6-dione (32)[13]

6,6-Ethylenedioxy-1,10β-dimethyl-$\Delta^{1,9}$-octal-2-one (50 g, 0.21 mole) was placed in a 1000-ml round-bottom flask equipped with a magnetic stirrer and condenser and containing 800 ml acetone and 0.5 g PTSA. The solution was stirred at reflux for 18 hr, cooled to room temperature, and 3 g solid $NaHCO_3$ was added. The solvent was removed under reduced pressure and the residue partitioned between benzene and water. The organic phase was separated and washed with three 100-ml portions of 5% aqueous $NaHCO_3$ solution and one 100-ml portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 30.5 g (75%) of 32: m.p. 98-99° (lit.[13] 103-104°); ir ($CHCl_3$) 1710, 1665 and 1620 cm^{-1}; nmr δ (CCl_4) 2.4 (br.m, 6H), 1.94 (m, 4H), 1.24 (s, 3H) and 1.75 ppm (s, 3H); λ max 244 nm (ε 11,800)

1,10β-Dimethyl-$\Delta^{1,9}$-octalin-2-one-6β-ol (33)[19]

1,10 β-Dimethyl-$\Delta^{1,9}$-octalin-2,6-dione (23.2 g, 0.12 mol) was dissolved in 150 ml absolute ethanol in a 500-ml three-necked flask

equipped with a magnetic stirrer, addition funnel, and a nitrogen inlet tube. The reaction mixture was cooled to 0° in an ice-salt bath and a solution of $NaBH_4$ (1.4 0.037 mol) in 100 ml absolute ethanol was added dropwise over a 1 hr period. The solution which became reddish brown was stirred for an additional hour at 0°. A solution of acetic acid in 20 ml ethanol was added dropwise until the solution turned yellow. The solvent was removed under reduced pressure and the residue was partitioned between water and ether. The ether layer was washed with two additional portions of water, dried over anhydrous $MgSO_4$, filtered, and the ether was removed under reduced pressure to give 20.2 g (87%) 33. An analytical sample recrystallized three times from hexane showed m.p. 96-96.5°; ir ($CHCl_3$) 3440, 1655, and 1600 cm^{-1}; nmr δ ($CDCl_3$) 4.89 (m, 1H), 4.68 (s, 1H) 2.48 (m, 6H), 1.80 (s, 3H), 1.85 (m, 4H), and 1.48 ppm (s, 3H); λ max 247 nm (ε 13,800).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.18; H, 9.35.
Found: C, 74.22; H, 9.44.

Esterification of 1,10 β-Dimethyl-$\Delta^{1,9}$-octalin-2-one-6-ol by Ethyl Malonyl Chloride

Sodium hydride (1.15 g, 0.023 mol), as a 50% mineral oil dispersion, was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, addition funnel, serum cap, and a nitrogen inlet tube. Three 50-ml portions of hexane were introduced, stirred, and the resulting solution was withdrawn by a long needle attached to a syringe in order to remove the mineral oil. Dry THF (150 ml, distilled from $LiAlH_4$) was added to the flask and 1,10 β-dimethyl- $\Delta^{1,9}$-octalin-2-one-6-ol (4.07 g, 0.021 mol) in 50 ml dry THF was added through the addition funnel

over a 10 min period. The solution was cooled to 0.5° in an ice-salt bath. Ethyl malonyl chloride (3.5 g, 0.023 mol) in 50 ml dry THF was added dropwise over a 30-min period. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was removed under reduced pressure and the residue taken up into 200 ml ether. The organic phase was washed with three 100-ml portions of 5% aqueous $NaHCO_3$ and 100 ml water. The organic solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 4.6 g (68%) of an orange oil 34. Attempted distillation in vacuo of a portion of the material led to decomposition with gas evolution. Attempted purification by column chromatography on silica gel and alumina was unsuccessful. The crude material showed the following spectral data: ir ($CHCl_3$) 1730, 1656, and 1609 cm^{-1}; nmr δ ($CDCl_3$) 4.21 (q, J = 7.0 Hz, 2H), 1.73 (s, 3H), 1.40 (s, 3H), and 1.24 ppm (t, J = 7.0 Hz, 3H).

Oxidation of 34 with Chloranil

The crude diester 34 (2 g, 6.5 mmol) was placed in a 250-ml round-bottom flask equipped with a magnetic stirrer and a reflux condenser with a nitrogen inlet tube. sec-Amyl alcohol (150 ml) and chloranil (7.8 g, 0.032 mol) were added and the mixture stirred at reflux overnight under a nitrogen atmosphere. The mixture was cooled, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with four 100-ml portions of 5% aqueous NaOH solution and one portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 0.7 g (34%) of 35 as

a black oil. Attempted distillation in vacuo of a small portion of the sample led to complete decomposition with gas evolution. Attempted purification of the product by column chromatography was unsuccessful. The following spectral properties were determined on the crude material: ir ($CHCl_3$) 1730, and 1660 cm^{-1}; nmr δ ($CDCl_3$) 6.71 (d, J = 10 Hz, 1H), 6.10 (d of d, J = 10 Hz and 4 Hz, 1H), 5.40 (m, 1H), 4.13 (q, J = 7.0 Hz, 2H), 1.76 (s, 3H), 1.25 (s, 3H), and 1.25 ppm (t, J = 7.0 Hz, 3H).

1,10 β-Dimethyl-$\Delta^{1,9,7,8}$-octalin-2,6-dione (37)

Reaction conditions were similar to those employed by Angello and Laubach.[21] 1,10 β-Dimethyl-$\Delta^{1,9}$-octalin-2,6-dione (5.2 g, 0.027 mol) was placed in a 500-ml flask equipped with a magnetic stirrer and a condenser with a nitrogen inlet tube. Chloranil (33.3 g, 0.135 mol) and 400 ml t-BuOH were added and the mixture was stirred at reflux for 3 hr under a nitrogen atmosphere. The reaction mixture was cooled, filtered, and the solvent removed under reduced pressure. The residue was dissolved in chloroform and washed consecutively with three portions of water, four portions of 5% aqueous NaOH solution, and three portions of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 4.3 g (83%) of the diene dione 37 as a yellow solid,: m.p. 79-82°. The material showed a single spot on TLC (silica gel/benzene) having an R_f value of 0.69. Spectral data were as follows: ir ($CHCl_3$) 1680, and 1668 cm^{-1}; nmr δ ($CDCl_3$) 7.49 (d, J = 9.5 Hz, 1H), 6.08 (d, J = 10.0 Hz, 1H), 2.48 (m, 4H), 2.09 (m, 2H), 1.92 (s, 3H), and 1.30 ppm (s, 3H); λ max 301 nm (ε 17,200).

Attempted Michael Reaction of 37 with Diethyl Sodiomalonate

Into a flame-dried 250-ml three-necked flask equipped with a magnetic stirrer, an addition funnel, and a condenser fitted with a nitrogen inlet tube, 100 ml ethanol was distilled from sodium and ethyl formate. Sodium (0.6 g, 0.026 mol) was dissolved in the ethanol and diethyl malonate (4.2 g, 0.026 mol) was added with stirring. The reaction mixture was cooled to 0-5° in an ice-salt bath and 1,10 β-dimethyl-$\Delta^{1,9,7,8}$-octalin-2,6-dione (5 g, 0.026 mol) in 25 ml anhydrous ethanol was added over a 30 min period. The mixture was stirred for 1 hr, warmed to room temperature, and stirred for an additional hour. Water (15 ml) was added and the solvent was removed under reduced pressure. The residue was partitioned between water and benzene and the organic phase was separated and washed with three portions of 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was a reddish oil whose nmr spectrum corresponded to a mixture of the starting materials. The starting diene dione 37 was recovered from the residue by crystallization from ether. When the reaction was repeated at reflux temperature with the same quantities of materials, a black tarry product was obtained. GLC analysis (column A, 100-200° @ 12°/min) showed eight peaks of comparable intensity. No effort was made to separate or identify these compounds.

Attempted Chloranil Oxidation of 1,10 β-Dimethyl-6,6-ethylenedioxy-$\Delta^{1,9}$-octal-2-one (31)

1,10 β-Dimethyl-6,6-ethylenedioxy-$\Delta^{1,9}$-octal-2-one (5 g, 0.021 mol) was placed in a 500-ml flask equipped with a magnetic stirrer and condenser with a nitrogen inlet tube. Chloranil (20.6 g, 0.084 mol) and t-butanol (250 ml) were added and the mixture was stirred at reflux for 18 hr under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and the excess chloranil removed by filtration. The solvent was then removed under reduced pressure and the residue partitioned between benzene and water. The organic phase was washed with three portions of 1% aqueous NaOH solution and one portion of water. The solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 3.5 g of a reddish brown precipitate found by infrared and nmr spectra to be identical with 37.

Enamine Alkylation of 1,10-β Dimethyl-$\Delta^{1,9}$-octalin-2,6-dione

Enamine formation was carried out according to the conditions used by Marshall et al.[226] 1,10 β-Dimethyl-$\Delta^{1,9}$-octalin-2,6-dione (78 g, 0.41 mol) was dissolved in 1000 ml dry benzene in a 2000-ml flask equipped with a magnetic stirrer, a Dean-Stark trap, and a condenser. Redistilled pyrollidine (40 g, 0.45 mol) was added and the solution stirred at reflux for 16 hr. Ethyl bromoacetate (83.5 g, 0.5 mol) was added to the mixture in small portions. The Dean-Stark trap was removed and the mixture stirred at reflux for 36 hr. One hundred milliliters of a 1% aqueous solution of acetic acid was added and the mixture stirred at reflux for an additional hour. The reaction mixture was cooled and the phases were separated. The organic phase was washed with three

250-ml portions of 10% HCl and one portion of water. The combined aqueous extracts were washed with 125 ml benzene. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. Unreacted starting material (55 g) was removed by trituration with 100 ml cold diethyl ether followed by filtration. The ether was removed from the filtrate under reduced pressure and the residue distilled in vacuo to give 19 g (56%) of ethyl (1,10β-dimethyl-2,6-dioxo-1-octal-7 β-yl) acetate (45): b.p. 190-196°; ir (thin film) 1730, 1720, 1665 and 1615 cm^{-1}; nmr δ (CCl_4) 4.08 (q, J = 7.0 Hz, 2H), 2.96 (m, 3H), 2.45 (m, 4H), 1.3 (m, 4H), 1.78 (s, 3H), 1.21 (s, 3H) and 1.21 ppm (t, J = 7.0 Hz, 3H); λ max 241 nm (ε, 12,000), m/e (70 ev) 278.1561 (calcd. 278.1517, 14%), 232 (30%), 190 (30%), 58 (100%), 43 (100%), and 15 (66%).

Anal. Calcd. for $C_{16}H_{22}O_4$; C, 69.06; H, 7.91. Found: c, 68.83; H, 8.02.

Reduction of Ethyl (1, 10β-Dimethyl-2,6-dioxo-1-octal-7 β yl)acetate

A. With Potassium Borohydride

Compound 45 (5 g, 0.018 mol) was dissolved in 150 ml dry methanol in a 500-ml three-necked flask equipped with a magnetic stirrer, an addition funnel, and a nitrogen inlet tube. The solution was cooled to 5° in an ice bath and potassium borohydride (0.25 g, 0.005 mol) in 100 ml dry methanol was added dropwise over a 30 min period under a nitrogen atmosphere. The reaction mixture was stirred at 5° for 30 min and at room temperature for 14 hr. The solvent was removed under reduced pressure and the residue partitioned between benzene and water. The

organic phase was washed with three portions of saturated brine solution. The organic layer was then dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 2.5 g of crude material. Infrared and nmr spectra of the crude material indicated that an approximately 1:1 mixture of enone lactone 46 and another product likely to be hydroxy ester 48 was present. Crystallization from 10 ml diethyl ether gave 1 g (25%) of enone lactone 46: m.p. 115-117°; ir ($CHCl_3$) 1775, 1663 and 1620 cm^{-1}; nmr δ ($CDCl_3$) 4.63 (m, 1H), 2.89 (m, 4H), 2.58 (br. m., 7H), 1.78 (s, 3H), and 1.30 ppm (s, 3H); λ max 243 nm (ε 10,300); m/e (70 ev) 234.1266 (calcd. 234.1251, 100%), 219 (66%), 216 (58%), 206 (61%), 192 (87%), 175 (69%), 174 (69%), 133 (86%), 132 (61%), 131 (72%), 119 (56%), 107 (55%), and 91 (52%).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.67; H, 7.75.

Spectra of the residue obtained from the mother liquor exhibited the following absorptions suggestive of hydroxy ester 48: ir ($CHCl_3$) 3450, 1730, 1665, and 1620 cm^{-1}; nmr δ 4.20 (q, J = 7.0 Hz), 1.16 (t, J = 7.0 Hz) and 1.09 (s) ppm. In addition, strong absorptions were observed corresponding to enone lactone 46. Composition of mixtures was determined by integration of the quartet at 4.20 ppm and comparison to the vinyl methyl signal at 1.78 ppm. A second determination compared integrations of the distinct bridgehead methyl signals at δ 1.30 and 1.09 ppm. Values of the two determinations agreed within 5%.

B. With Triisobutylaluminum

Compound 45 (0.5 g, 1.8 mmol) was placed in a flame-dried 100-ml three-necked flask equipped with a magnetic stirrer and a condenser

fitted with a nitrogen inlet tube. Dry benzene (50 ml, distilled from sodium) and a benzene solution of triisobutylaluminum (1.8 ml, 1.11 M) were introduced at room temperature and the solution was stirred at reflux for 36 hr under a nitrogen atmosphere. The mixture was cooled to room temperature, filtered, and washed with three 25-ml portions of 5% HCl solution and one 25-ml portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue (0.4 g) was analyzed by nmr spectroscopy and showed an approximately 7:3 ratio of lactone to hydroxyester. Recrystallization from diethyl ether gave 100 mg of the lactone 46.

C. With Potassium Tri-sec-butylborohydride (Potassium Selectride)

A solution of 45 (16.0 g 0.022 mol) in 150 ml dry THF (distilled from $LiAlH_4$) was placed in a 250-ml flask equipped with a magnetic stirrer, a nitrogen inlet tube, and a rubber septum. The solution was cooled to -78° in a dry ice-acetone bath and Potassium Selectride (51 ml, 25.8 mmol, 0.5 M solution purchased from Aldrich Chemical Company) was added dropwise by a syringe over a 30 min period. A deep purple color appeared soon after addition was begun. The solution was stirred at -78° for 4 hr and 18 ml of a 3 N KOH solution was added with vigorous stirring. The mixture was allowed to warm to room temperature and stirred while being exposed to the atmosphere for 4 hr. The solution was transferred to a 500-ml Erlenmeyer flask, 80 ml of a 3 N HCl solution was added, and the solution was stirred for one hour. The volume was reduced to approximately 100 ml under reduced pressure and the mixture was extracted with three 50-ml portions of benzene. The combined organic extracts were washed with three portions of 10% aqueous NaCl

solution, dried over anhydrous $NaHCO_3$, and filtered. Removal of the benzene under reduced pressure gave 4.7 g of a crude product. Nmr spectroscopy showed no detectable quantity of the hydroxy-ester. Recrystallization from diethyl ether gave 2.7 g (54%) of reasonably pure lactone, m.p. 193-195°. An initial crop of crystals was obtained by alternately cooling the solution to -20° and rewarming to room temperature while scraping the bottom of the container with a spatula. The mother liquor was then allowed to evaporate at -20° and the oily crystals which were formed were washed with additional cold ether.

Ketalization of (1,10 β-Dimethyl-2-oxo-6β-hydroxy-1-octal-7 β-yl)acetic Acid Lactone

The enone lactone 46 (1 g, 4.3 mmol) was dissolved in 100 ml dry benzene in a 250-ml flask equipped with a magnetic stirrer and a Dean-Stark trap with a condenser fitted with a nitrogen inlet tube. The Dean-Stark trap was half-filled with anhydrous K_2CO_3. Ethylene glycol (10.3 g, 0.166 mol) and PTSA (30 mg) were added to the flask and the mixture sitrred at reflux for 14 hr. The solution was cooled and 2 ml of pyridine and 4 g of $NaHCO_3$ were added. The benzene solution was washed consecutively with water, 5% aqueous $NaHCO_3$ solution, and a 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give 1.1 g (90%) of the ketal 49 as a cream colored solid: m.p. 167-169°; ir ($CHCl_3$) 1770 cm^{-1}; nmr δ ($CDCl_3$) 5.13 (br. S, 1/2 H) 3.94 (s, 4H), 1.64 (s, 3H), 0.80 and 0.88 (s, 3H); m/e (70 ev) 278.1504 (calcd. 278.1512).

Hydroxymethylation of (1,10 β-Dimethyl-2,2-ethylenedioxy-6 β-hydroxy-1-octal-7 β-yl)acetic Acid Lactone

Reaction conditions were similar to those employed by Grieco.[24] Dry THF (200 ml, distilled from $LiAlH_4$) was introduced into a flame-dried 500-ml three-necked flask equipped with a magnetic stirrer, dry ice-acetone bath, rubber septum, and an inlet from a paraformaldehyde pyrolysis apparatus. 2,2-Bipyridyl (30 mg) was added as an indicator. Phenyllithium in benzene solution (2.7 ml, 0.0052 mol) was transferred into the flask with a syringe. The solution was cooled to -78° and dry diisopropylamine (1 ml, 0.0064 mol, distilled from CaH_2) was added slowly with a syringe. After the reaction mixture had been stirred for 45 min., 1.2 g (0.0043 mol) of the ketal lactone 49 in 60 ml THF was added. The solution was stirred at -78° for 30 min and then allowed to warm to -20°. Gaseous formaldehyde, obtained by immersing the pyrolysis apparatus containing paraformaldehyde in an oil bath having a temperature of 160°, was passed over the stirred solution in a stream of nitrogen for 5 min. A color change from brownish-red to bright yellow was observed. Water (2 ml) was added, the mixture was warmed to room temperature, and the solvent removed under reduced pressure. The residue was partitioned between 100 ml benzene and 50 ml water. The organic phase was washed with three 25-ml portions of saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give 1.1 g (85%) of the hydroxymethyl compound 50: ir (thin film) 3450 and 1757 cm^{-1}; nmr δ ($CDCl_3$) 5.22 (s, 0.5H), 3.94 (s, 2H), and 3.88 ppm (s, 2H), 1.63 (s 3H), and 1.20 ppm (s, 3H). No molecular ion was observed in the mass spectrum, but a peak at m/e 290 (m-18) was observed.

Dehydration of Hydroxymethyl(1,10 β-Dimethyl-2,2-ethylenedioxy-6 β-hydroxy-1-octal-7 β-yl) acetic Acid Lactone

Hydroxymethyl lactone 50 (1 g, 3.2 mmol) prepared as described above was dissolved in 25 ml anhydrous pyridine (distilled from BaO and stored over 4Å molecular sieves) in a 100-ml flask equipped with a rubber septum, magnetic stirrer, and ice bath. After cooling to 0°, methanesulfonyl chloride (0.7 g, 6 mmol) was added with stirring under a nitrogen atmosphere. The solution gradually turned dark brown. The rubber septum was replaced by a condenser and the reaction mixture stirred at reflux for 6 hr. The pyridine was removed under reduced pressure and the black residue partitioned between benzene and water. The organic phase was washed with three portions of 10% aqueous NaCl solution, dried over anhydrous $MgSO_4$, and filtered. Removal of the benzene under reduced pressure gave 0.69 g (74%) α-methylene lactone 52 as a dark oil: ir (thin film) 1761 and 1622 cm^{-1}; nmr δ ($CDCl_3$) 6.14 (d, J = 2.0 Hz, 1H) 5.61 (d, J = 1.5 Hz, 1H), 5.11 (m, 0.5 H), 4.70 (m, 1H), 3.86 (s, 4H) and 1.15 ppm (s, 3H); m/e 290 peak was observed in the mass spectrum but was too small to permit an accurate exact mass determination.

Deketalization of α-Methylene-(1,10 β-Dimethyl-2,2-ethylenedioxy-6 β-hydroxy-1-octal-7 β-yl)acetic Acid Lactone

A solution of 540 mg (1.8 mmol) of the α-methylene lactone 52 in 75 ml of reagent grade acetone was placed in a 100-ml flask equipped with a magnetic stirrer and condenser fitted with nitrogen inlet tube

PTSA (50 mg) was added and the reaction mixture stirred at reflux for 12 hr under nitrogen. The solution was cooled to room temperature, 0.5 g of $NaHCO_3$ was added, and the acetone removed under reduced pressure. The residue was dissolved in benzene, washed with saturated aqueous NaCl solution, and the aqueous phase extracted with 30 ml benzene. The combined benzene layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude yellow oil was chromatographed on Florisil and the fractions eluted with 30-50% chloroform/benzene were collected to give 200 mg (45%) of the α-methylene lactone 52: m.p. 164-165°. The material was recrystallized from a chloroform-ether mixture to give a product having the following spectral data: ir ($CHCl_3$) 1764, 1660 and 1625 cm^{-1}; nmr δ ($CDCl_3$) 6.40 (d, J = 2.8 Hz, 1H), 5.78 (d, J = 2.4 Hz, 1H), 4.64 (m, 1H), 1.83 (s, 3H) and 1.25 ppm (s, 3H); λ max 246 nm (ε 14,500); m/e (70 ev) 246.1245 (calcd. 246.1255, 100%), 204 (68%), 108 (60%), 93 (42%), 91 (61%), 79 (45%) 77 (44%), 53 (50%), 41 (47%).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37.
Found: C, 73.03; H, 7.36.

(±) Yomogin (53)

A solution of 160 mg (0.65 mmol) of the α-methylene lactone 52 in 30 ml of dry dioxane (distilled from sodium) was placed in a 50-ml flask equipped with a magnetic stirrer and a condenser fitted with a nitrogen inlet tube. 2,3-Dichloro-5,6-dicyana-1,4-benzoquinone (DDQ 160 mg, 0.71 mmol) was added and the reaction mixture was stirred at reflux for 18 hr under nitrogen. The mixture was cooled to room temperature, the precipitate of 2,3-dichloro-5,6-dicyanohydroquinone separated

by filtration, and the dioxane removed from the filtrate under reduced pressure. The residue was dissolved in benzene and the solution extracted with four 25-ml portions of 1% aqueous NaOH solution and one 25-ml portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was crystallized from diethyl ether to give 100 mg (62%) crude crystalline (±)-yomogin. An analytical sample was recrystallized from an ether-chloroform mixture to give pure material with the following properties: m.p. 181-182°; (lit. 201-202)[25]; ir ($CHCl_3$) 1768, 1662, 1630 and 1612 cm^{-1}; nmr δ ($CDCl_3$) 6.80 (d, J = 10.0 Hz, 1H), 6.22 (d, 1.5 Hz, 1H), 6.18 (d, J = 10.0 Hz, 1H), 5.76 (d, J = 1.5 Hz, 1H), 4.54 (m, 1H) 1.95 (s, 3H) and 1.30 ppm (s, 3H); m/e (70 ev) 244.1126 (calcd. 244.1099). The infrared, nmr, and the mass spectra of the synthetic material were identical with a sample of the natural product.[25] TLC on silica gel (Eastman sheets) showed that the two samples had identical Rf values of 0.13 in benzene and 0.28 in chloroform.

DDQ Oxidation of (1,10 β-Dimethyl-2-oxo-6 β-hydroxy-1-octal-7 β-yl)acetic Acid Lactone

A solution of the enone lactone 46 (0.8 g, 3.4 mmol) (freshly distilled from sodium) and 0.9 g, 3.7 mmol of DDQ in 50 ml of dry dioxane was added to a 100-ml flask equipped with a magnetic stirrer and condenser fitted with a nitrogen inlet tube. The mixture was stirred at reflux for 18 hr under nitrogen. The solution was cooled to room temperature, filtered, and the dioxane removed from the filtrate under reduced pressure. The residue was dissolved in 50 ml of benzene and washed with four 25 ml portions of 1% aqueous KOH solution followed by one 25 ml

portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the benzene was removed under reduced pressure. The residue was crystallized from diethyl ether to give 0.275 g (35%) of the dienone lactone 56: m.p. 196-197°; ir ($CHCl_3$) 1774, 1662, 1628 and 1606 cm^{-1}; nmr δ ($CDCl_3$) 6.90 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 10.0 Hz, 1H), 4.66 (m, 1H), 2.58 (br.m, 6H), 1.96 (s, 3H) 1.75 (m, 1H) and 1.37 ppm (s, 3H); λ max 238 nm (ϵ 11,100). No molecular ion was observed in the mass spectrum. m/e (70 ev): 172 (57%), 144 (91%), 120 (61%), 105 (55%), 91 (66%), 77 (74%), 65 (61%), 51 (55%), 41 (100%, 39 (88%).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90.
Found: C, 72.33; H, 6.99.

Photolysis of (1,10-Dimethyl-2-oxo-6β hydroxy-1,3-octal-7-yl) acetic Acid Lactone (56)

Dienone lactone 56 (250 mg, 1.07 mmol) was dissolved in 10 ml glacial acetic acid in a Pyrex test tube. The tube was clamped into a photolysis apparatus and nitrogen was bubbled rapidly through the solution to provide vigorous agitation. The solution was irradiated for 3 hr using a 450-watt Hanovia high pressure mercury lamp. The acetic acid was removed by lyophilization and the residue was chromatographed on florisil. The fractions eluted by chloroform was characterized by the nmr spectral analysis as containing only the starting material (50 mg total recovered). The fractions eluted by 4-10% methanol in chloroform were collected and crystallized from diethyl ether to give 120 mg (50%) of the 5/7-fused photo produce 60: m.p. 140-141°; ir ($CHCl_3$) 1771, 1721, 1701, and 1640 cm^{-1}; nmr δ ($CDCl_3$) 5.26 (m, 1H), 3.60 (m, 1H), 2.45 (d, J = 3.8 Hz, 2H), 2.00 (s, 3H), 1.70 (br s, 3H), and 1.25 ppm (s, 3H).

Irradiation of the signal at 3.60 caused the collapse of the signal at δ 2.45 to a singlet and sharpening of the signal at δ 1.70. No molecular ion was observed in the mass spectrum, but an m/e 232 (M-60, 32%) peak was present. Other peaks were observed at m/e (70 ev) 85 (40%), 83 (63%), 55 (23%), 43 (100%), and 41 (31%).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.72; H, 6.90.
Found: C, 65.81; H, 6.93.

Attempted Hydroxylation of Dienone Lactone 56

A. In Acetic Acid

The reaction was carried out under conditions used by Abe, et. al.[26] A solution prepared from 200 mg (0.86 mmol) of the dienone lactone 56, 5.0 ml of glacial acetic acid, 100 mg (0.91 mmol) of freshly prepared and resublimed selenium dioxide, and 0.5 ml of water was stirred at reflux under nitrogen for 18 hr. The reaction mixture was cooled to room temperature and 400 mg Celite was added with stirring. The mixture was filtered and the solvent removed under reduced pressure. The infrared and nmr spectra of the crude product indicated that only starting material was recovered.

B. In Dioxane

The reaction was carried out under conditions used by Furlemmeier, et al.[27] A solution prepared from 100 mg (0.44 mmol) of dienone lactone 56, 25 ml of dioxane, and 100 mg (0.91 mmol) of freshly sublimed selenium dioxide was stirred at 90° for 4 days. Celite (300 mg) was added with stirring and the slurry was filtered. The dioxane was removed from the filtrate under reduced pressure; the residue was mixed with 5 ml water and filtered. A red granular precipitate having infrared and nmr spectra

corresponding to the starting material was obtained.

C. In t-Butyl Alcohol

A solution prepared from 200 mg (0.88 mmol) of the dienone lactone 56, 25 ml of dry t-butyl alcohol (freshly distilled from sodium), 400 mg (3.64 mmol) of selenium dioxide and one ml of glacial acetic acid was stirred at reflux under nitrogen for 5 days. The reaction mixture was cooled to room temperature, 50 mg Celite was added, and the mixture was filtered. The solvent was removed from the filtrate under reduced pressure to give a residue identified spectrally as the starting material.

Enol Acetylation of (1,10β-Dimethyl-2-oxo-6β-hydroxy-1-octal-7β-yl)acetic Acid Lactone

Enone lactone 45 (1.5 g, 6.4 mmol) was dissolved in 15 ml acetic anhydride (freshly distilled through an 18-inch Vigreaux column, b.p. 138°) and placed in a 25-ml flask equipped with an oil bath, magnetic stirrer, and nitrogen inlet. Two drops of concentrated sulfuric acid were added and the solution was observed to turn light red. The mixture was heated to 55° and stirred at that temperature for 4 hr. The solvent was removed under reduced pressure and the residue dissolved in benzene. The solution was washed with water, three portions of 5% aqueous $NaHCO_3$ solution, and 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from acetone to give 800 mg (45%) of the enol acetate 58: m.p. 149-150°; ir ($CHCl_3$) 1771 and 1752 cm^{-1}; nmr δ ($CDCl_3$) 5.40 (d, J = 2.0 Hz, 1H), 4.95 (m, 1H), 3.44 (m, 1H), 3.16 (m, 1H), 2.6 (br, m, 5H) 2.06

(m, 2H), 1.54 (s, 3H), 2.18 (s, 3H), and 1.15 ppm (s, 3H); m/e (70 ev) 276.1349 (calcd. 276.1362, 14%) 235 (32%), 234 (60%), 192 (27%), 91 (18%), 43 (100%), 41 (22%), 40 (24%). UV λ max (95% ethanol) 236 nm, (ε 26,000).

Anal. Calcd. for $C_{16}H_{20}O_4$; C, 69.56; H, 7.25. Found: C, 69.54 H, 7.29.

Purification of m-Chloroperbenzoic Acid[28]

A pH 7.5 buffer solution was prepared by mixing 100 ml. Potassium dihydrogen phosphate solution (0.1 M) and 81.8 ml, 0.1 M hydroxide solution. Crude m-chloroperbenzoic acid was washed with the buffer solution for 15 minutes. The slurry was filtered and the solid dried in vacuo. The dry peracid (0.345 g, 2.0 mmol) was dissolved in glacial acetic acid and 10 ml 20% aqueous KI solution was added. The solution was allowed to stand in the dark for 15 min and then titrated with 0.100 N sodium thiosulfate solution to the starch iodide end point. The strength of the peracid was found to be 86%.

Attempted Epoxidation of Enol Acetate 58

A. With m-Chloroperbenzoic Acid

Enol acetate 58 (700 mg, 2.5 mmol) was dissolved in 50 ml methylene chloride in a 250-ml flask equipped with a magnetic stirrer, rubber septum, and a condenser fitted with a nitrogen inlet tube. m-Chloroperbenzoic acid (567 mg, 2.7 mmol) in 20 ml methylene chloride was added dropwise over a 10-min. period. The solution was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was extracted with four 25-ml portions of 5% aqueous $NaHCO_3$ solution

and one portion of 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Infrared and nmr spectra indicated that only the starting material was recovered.

Under more severe conditions (8 hr in methylene chloride at reflux) a product was obtained which showed anomalous peaks in the aromatic region of the nmr spectrum while the vinyl methyl peak was absent. In the infrared spectrum a 1730 cm^{-1} peak was observed but no peak was seen in the 1665 cm^{-1} region for the α,β -unsaturated carbonyl group.

B. With Performic Acid

Conditions for this reaction are similar to those used by Abe, et al.[26] Enol acetate 58 (100 mg, 0.36 mmol), 4.5 ml redistilled formic acid, 0.5 ml water, and four drops 30% H_2O_2 solution were mixed in a 25-ml flask fitted with a magnetic stirrer and a condenser fitted with a nitrogen inlet tube. The reaction mixture was stirred for 4 hr at room temperature under a nitrogen atmosphere. The formic acid was removed under reduced pressure and the residue partitioned between 25 ml benzene and 25 ml 10% NaCl solution. The organic phase was washed with two portions of aqueous $NaHCO_3$ solution and one portion of 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the benzene was removed under reduced pressure. The residue was identified as starting material on the basis of its infrared and nmr spectra.

Standardization of Lead Tetraacetate[29]

Lead tetraacetate (505 mg) was dissolved in 5 ml glacial acetic

acid by gentle application of heat. A solution of 12.0 g anhydrous sodium acetate and 1.0 g potassium iodide in 100 ml water was added to the solution. The solution was titrated with 0.100 N sodium thiosulfate solution to the starch iodide end point. The percentage of lead tetraacetate was calculated by the formula:

$$\% \text{ Pb } (OAc)_4 = 2.217 \left(\frac{\text{ml. thiosulfate soln.}}{\text{wt. of sample}}\right)$$

Using the data obtained, the strength of the lead tetraacetate was found to be 97%. It was therefore decided that purification of the commercial material was not necessary.

Attempted Oxidation of Enol Acetate 58 With Lead Tetraacetate

Conditions used in this reaction were similar to those used by Nambara and Fishman.[30] Enol acetate (100 mg., 0.36 mmol) was dissolved in 3 ml glacial acetic acid containing three drops acetic anhydride in a 10-ml predried round-bottom flask equipped with a magnetic stirrer and a nitrogen inlet tube. Lead tetraacetate (182 mg, 0.39 mmol) was added and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue dissolved in 25 ml benzene. The benzene was washed with 10 ml 10% aqueous NaCl solution and the benzene layer dried over anhydrous $MgSO_4$, filtered, and the benzene was removed under reduced pressure. The nmr spectrum showed only the presence of the starting material.

When the experiment was repeated with the solution temperature at 80° for 12 hr the product was a dark oil which showed four spots

on TLC (silica gel/$CHCl_3$). The nmr spectrum of the recovered material did not show an absorption in the vinyl methyl region and the infrared spectrum did not show an appreciable absorption characteristic of an α,β-unsaturated carbonyl group.

Attempted Hydroxylation of the 5/7-Fused Photoproduct 60

Photoproduct 60 (100 mg, 0.34 mmol) was dissolved in 20 ml dioxane containing 3 drops of water in a 50-ml flask equipped with a magnetic stirrer and reflux condenser. Selenium dioxide (100 mg, 0.90 mmol, freshly sublimed) was added and the mixture was heated with stoving at 95° in an oil bath for 48 hr. The mixture was cooled, 300 mg Celite was added, and the mixture filtered through a layer of Celite. The solvent was removed under reduced pressure and the residue partitioned between benzene and 10% aqueous NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. Thin layer chromatography of the crude product on silica gel showed the presence of at least five significant compounds and the nmr spectrum of the mixture appeared too complex for interpretation. No absorption was observed in the hydroxyl stretching region of the infrared spectrum.

Epoxidation of Enol Acetate 58

Enol acetate 58 (200 mg, 0.71 mmol) was placed in a 100-ml flask equipped with a magnetic stirrer, septum, and nitrogen inlet. Methylene chloride (20 ml) was added and a solution of 275 mg (0.83 mmol) m-chloroperbenzoic acid (purified by washing with pH 7.5 buffer) in 20 ml methylene chloride was added with stirring over a 10 min period. The

reaction mixture was stirred for 5 hr at room temperature under a nitrogen atmosphere. The solution was extracted with four portions of 5% aqueous Na_2CO_3 solution and one portion of 10% aqueous NaCl solution. The organic phase was stirred with anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 100 mg of a sticky white solid. Thin layer chromatography on silica gel showed three spots at Rf values 0.71, 0.22, and the origin. Preparative thin layer chromatography gave 80 mg the non-polar material but the nmr spectrum showed no correlation with the expected structure. The two polar materials were not completely separated and gave a total of 60 mg of material having an nmr spectrum virtually identical to the starting material except that the vinyl hydrogen signal at 5.40 ppm had disappeared. Infrared absorptions at 1771 and 1775 cm^{-1} ($CHCl_3$) were observed.

Attempted Hydrolysis of the Epoxidation Product of Enol Acetate 58

The crude product from the above reaction (60 mg, 0.2 mmol) was placed in a 50-ml round bottom flask equipped with a magnetic stirrer and reflux condenser. Dioxane (15 ml) and water (2 ml) were added. Oxalic acid (40 mg, 0.45 mmol) was added, the mixture stirred overnight at room temperature, then heated to 70° for 1 hr in an oil bath. The solvent was removed under reduced pressure and the residue dissolved in 20 ml benzene. The solution was extracted with four portions of satd. aqueous $NaHCO_3$ solution and one portion of water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 40 mg of a cream colored solid. The infrared

spectrum showed no absorption corresponding to a hydroxyl group and the absorption at 1754 cm^{-1} remained, indicating that the compound was starting material.

CHAPTER IV

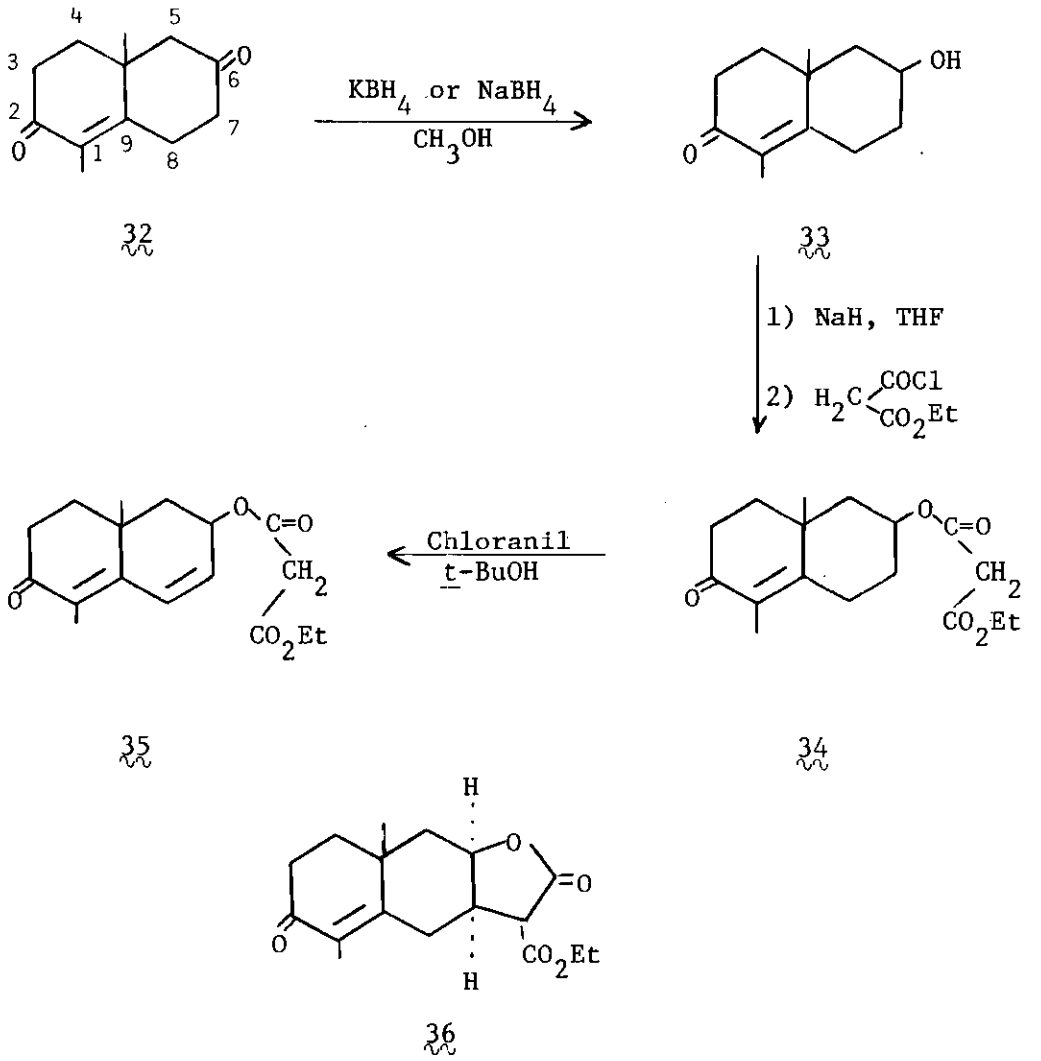
Discussion of Results

The synthesis of the starting material, 1,10β-dimethyl-$\Delta^{1,9}$-octalin-2,6-dione, has been previously reported.[13] However, in our experience, several steps in the published procedures required adjustment of conditions to obtain acceptable yields. Therefore, a discussion of the preparation of the starting material would seem relevant.

Knoevenagel condensation of furfural with malonic acid proceeded normally to give an 85% yield of β-furyl-acrylic acid 27. Reaction of 27 with gaseous hydrogen chloride in ethanol seemed to proceed normally only if passage of the hydrogen chloride was initiated before heating and the heat of reaction was allowed to bring the solution to reflux temperature. If external heat was applied prematurely, an anomalous low boiling product was recovered. Under proper conditions a 60% yield of diethyl-γ-oxopimelate 28 was obtained. Ketalization of 28 proceeded uneventfully but separation of the product from the unreacted starting material posed a problem. The ketal-diester 29 was not very stable to heat and on distillation about one third of the material remained as a viscous nonvolatile residue.[31] The problem was minimized by carrying out the distillation as rapidly as possible. Under optimum conditions, a yield of 83% of diethyl-γ,γ-ethylenedioxypimelate 29 was obtained. Dieckmann cyclization, methylation, and base hydrolysis under proper conditions gave 50% yields of 2-methyl-4,4-ethylenedioxycyclohexanone 30. However, yields varied drastically from batch to batch and appeared

to depend on the quality of the sodium hydride used in the reaction. Robinson annelation of 30 was carried out according to the procedure of Ross and Levine.[18] Good yields of 6,6-ethylene-dioxy-1,10 β-dimethyl-$\Delta^{1,9}$-octal-2-one 31 were obtained. Transketalization with PTSA and acetone gave an 85% yield of 1,10 β-dimethyl-$\Delta^{1,9}$-octalin-2,6-dione 32. However, the published procedure[13] had to be modified so that the PTSA was neutralized before the workup. Without this modification, low yields of impure product were obtained.

Functionalization of the C-7 position of 32 was attempted via the internal Michael reaction sequence depicted in Scheme 7. Hydroxy enone 33 was fully characterized. However, subsequent products in this sequence were not sufficiently stable to allow purification.



32 33 34 35 36

Scheme 7.

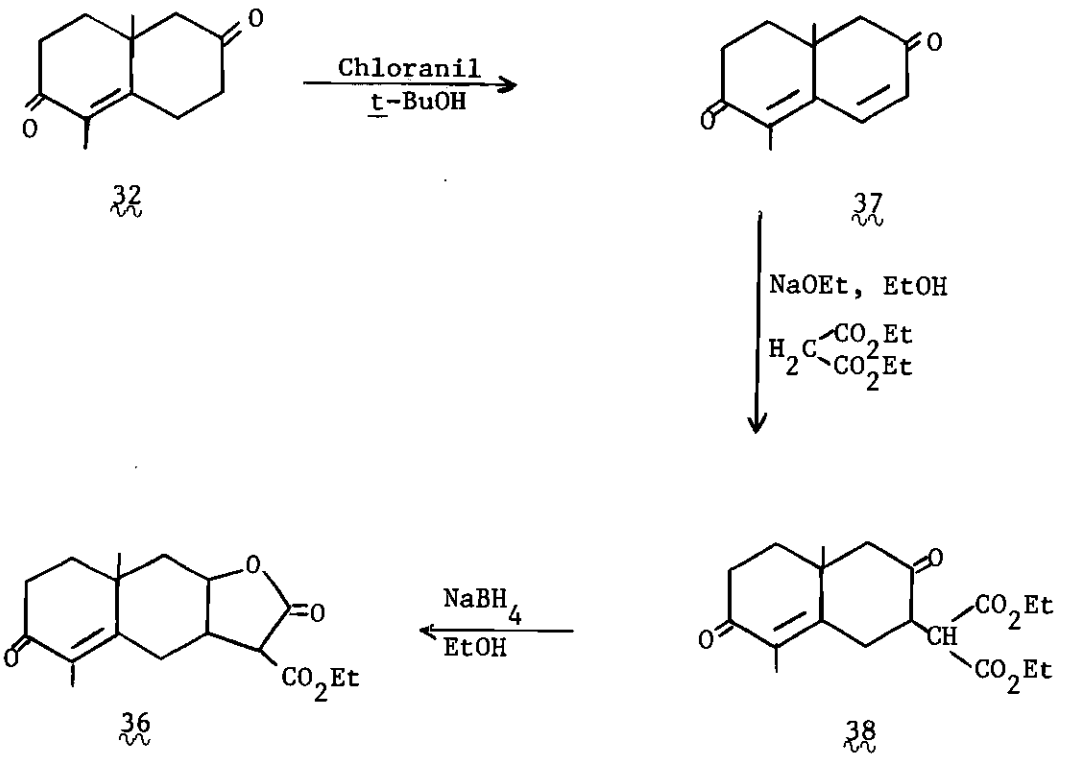
Sodium borohydride reduction of enedione 32 gave fair yields of enone alcohol 33. Selective reduction of the C-6 carbonyl group was indicated by the disappearance of the 1710 cm^{-1} peak and maintenance of the 1665 cm^{-1} peak in the infrared spectrum of the hydroxy enone product. The sterochemistry at C-6 was assigned because a downfield shift of the C-10 methyl signal from 1.25 ppm to 1.48 ppm occurred in the nmr spectra

in going from the 6-keto to the 6-hydroxy compound. This shift results from the introduction of a 1,3-diaxial interaction of the angular methyl group with the β-hydroxyl group at C-6. Analogous results were observed with steroid systems.[32]

Esterification of 33 with ethyl malonyl chloride gave a crude product corresponding to structure 34. The infrared and nmr spectra were consistent with this structure. However, attempted distillation of the crude product resulted in extensive decomposition with gas evolution. Likewise, chromatographic purification of the compound was unsuccessful. The crude material was oxidized with chloranil to give a dark oil which corresponded to 35. A vinyl hydrogen signal was observed at 6.10 ppm as a doublet of doublets which was assigned to the vinyl proton at C-7. A doublet at 6.71 ppm was assigned to the C-8 vinyl proton. This evidence suggested that the new double bond was in linear conjugation rather than cross conjugated.

All attempts to purify 35 met with failure. Since two intermediates in this sequence were not readily purified, this approach to the lactone intermediate 36 was abandoned. In retrospect, the intramolecular Michael reaction might not have been successful due to poor orbital alignment in the linearly conjugated system. Also, formation of the five-membered lactone ring may be a geometrically unfavorable process.

It was questioned at this point whether an intermolecular Michael reaction might not be effective in functionalizing the 7-position of the bicyclic system. Scheme 8 portrays a possible approach.

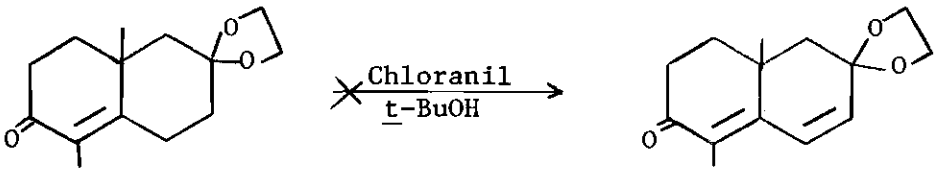


Scheme 8.

Chloranil oxidation of 32 proceeds with facility to give the fully conjugated diene diketone 37 in 58% yield. However, under mild conditions, Michael addition of diethyl sodiomalonate anion to 37 did not occur and only starting material was recovered. Under more severe conditions, a complex mixture of products was obtained which indicates that extensive rearrangements had probably occurred. Failure of 37 to undergo normal Michael reaction is probably due to opposing polarities of the carbonyl groups. Also, disruption of the fully conjugated system may require the expenditure of a large amount of energy. It is interesting to note that this compound failed to undergo hydrogenation with homogeneous catalyst while cross-conjugated dienones readily hydrogenate

under these conditions.[33]

It was thought that replacement of the C-6 carbonyl by a ketal function would facilitate the intermolecular Michael reaction. However, an attempt to prepare the 6,6-ethylenedioxy compound by oxidation of the enone ketal 31, as shown in Scheme 9, was unsuccessful.

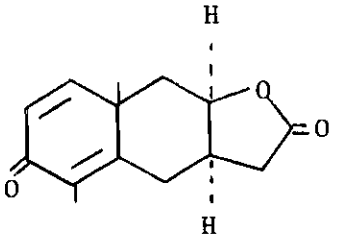


31 40

Scheme 9.

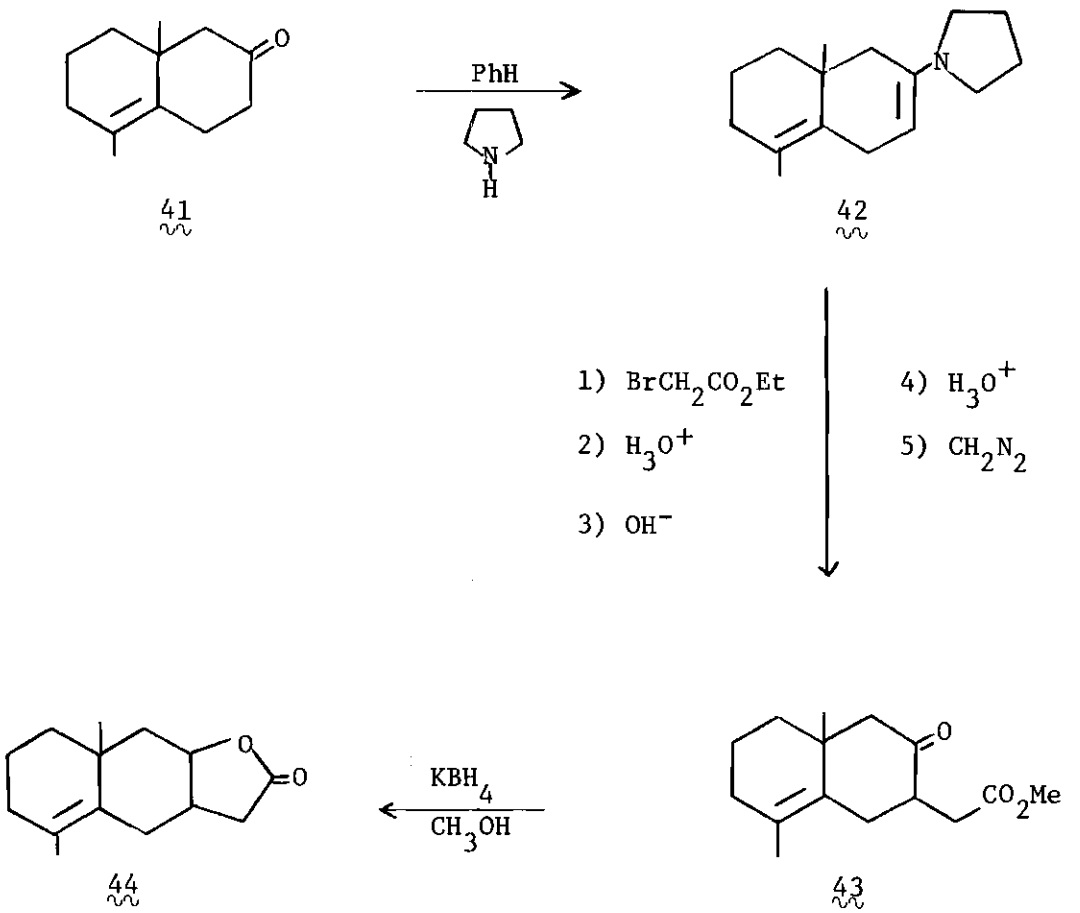
The only isolable product from the reaction had spectral properties identical to diene diketone 37. Evidently, the hydroquinone from DDQ is sufficiently acidic to cause hydrolysis of the ketal functionality. The Michael reaction approach to the functionalization of C-7 was abandoned at this point.

Another reasonable precursor for the synthesis of euparotin appeared to be the enone lactone 46 which hopefully could be hydroxylated at C-8 during a later stage of the synthesis.



46

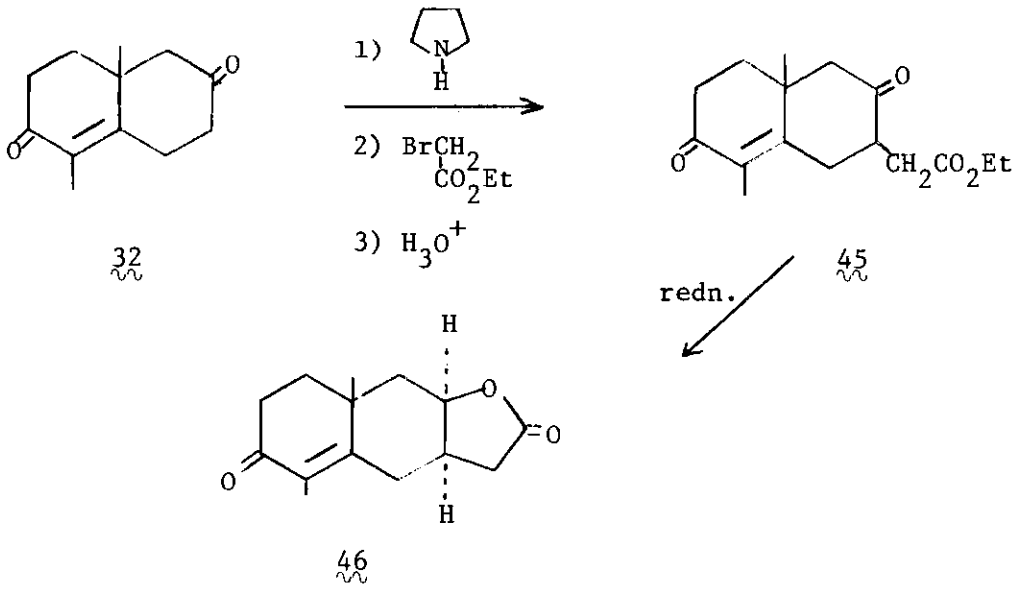
The 2-deoxy derivative of 46, i.e. 44, has been prepared previously by Marshall and coworkers in their synthesis of dl-alantolactone and dl-telekin.[22b] The route to 44 employed by these workers is shown in Scheme 10. It involves the preparation and alkylation of the enamine 42 as a means of introducing the acetic acid side chain at C-7. Marshall inferred that the enamine formed toward C-7 (rather than C-5) by analysis of the nmr spectrum of the intermediate. Alkylation with ethyl bromoacetate followed by hydrolysis led to an ethyl ester product which was hydrolyzed and reesterified with ethereal diazomethane to produce the methyl ester 43. Potassium borohydride reduction of 43 gave the cis γ-lactone 44 in 74% yield.



Scheme 10.

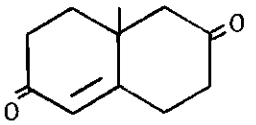
It seemed possible that on treatment of 32 with one equivalent of pyrrolidine it might be possible to selectively form the enamine of the saturated ketone function. It was expected that this enamine might be more stable than the one derived from functionalization of the α -substituted α , β -unsaturated carbonyl group because of the interaction of the α -methyl substituent with the methylene group of the pyrrolidine ring. It was also anticipated that the formation of the saturated ketone might be favored kinetically. Indeed, selective alkylation at C-7 of 32 was found to be possible. Treatment of this

compound with one equivalent of pyrrolidine in benzene under the conditions employed by Marshall and coworkers[22b] which were based upon the original procedure of Stork and coworkers[34] gave a dark solution of the enamine which was alkylated in situ with excess ethyl bromoacetate and hydrolyzed to give a 56% yield of the ketoester 45 (see Scheme 11). The product showed the expected spectral properties including an infrared absorption at 1730 cm^{-1} and nmr absorptions at δ 4.08 (q, J = 7.0 Hz) and 1.21 (t, J = 7.0 Hz) attributed to the ethyl ester grouping.



Scheme 11.

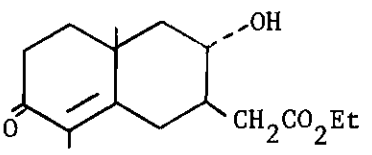
It should be noted that attempted application of the same enamine alkylation sequence to the ketoenone 47 in which the 1-methyl group is absent was unsuccessful and only the starting material and high molecular weight polymeric material was observed.



47

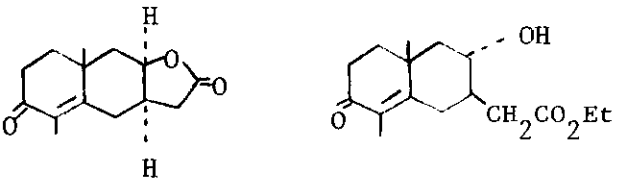
This observation would suggest that the α-methyl substitution may be more important in preventing enamine formation than the conjugated nature of the carbonyl group.

Initial efforts at reduction of 45 were directed toward the use of potassium borohydride in methanol. Marshall[22b] has reported that reduction of 43 occurred preferentially from the α side of the molecule to give 74% of the desired 6β,7β-lactone. In our hands, the reduction of 45 proved to be non-stereoselective giving roughly equal amounts of 46 and another component presumed to be hydroxy ester 48. Infrared absorptions at 3450 and 1730 cm^{-1} as well as nmr signals at 4.20 (q, J = 7.0 Hz), 1.16 (t, J = 7.0 Hz), and 1.09 (s) ppm supported the structural assignment of 48. Composition of the mixture was determined by integration of the nmr spectrum (see Experimental).



48

Surprisingly, the two compounds were not separable by thin layer or column chromatography. An additional complication was that only half of the lactone 46 could be crystallized from the mixture in diethyl ether. Apparently, the hydroxy ester 48 has a solubilizing effect on the lactone. A solution to this problem appeared to be the use of a more bulky reducing agent to minimize formation of 48. Reduction with triisobutyl aluminum and potassium tri-sec-butylborohydride (Potassium Selectride) were investigated and the results are summarized in Scheme 12.



Potassium borohydride:

Composition by nmr	1	:	1
Isolated yield	25%		

Triisobutylaluminum:

Composition by nmr:	7	:	3
Isolated yield	25%		

Potassium Selectride:

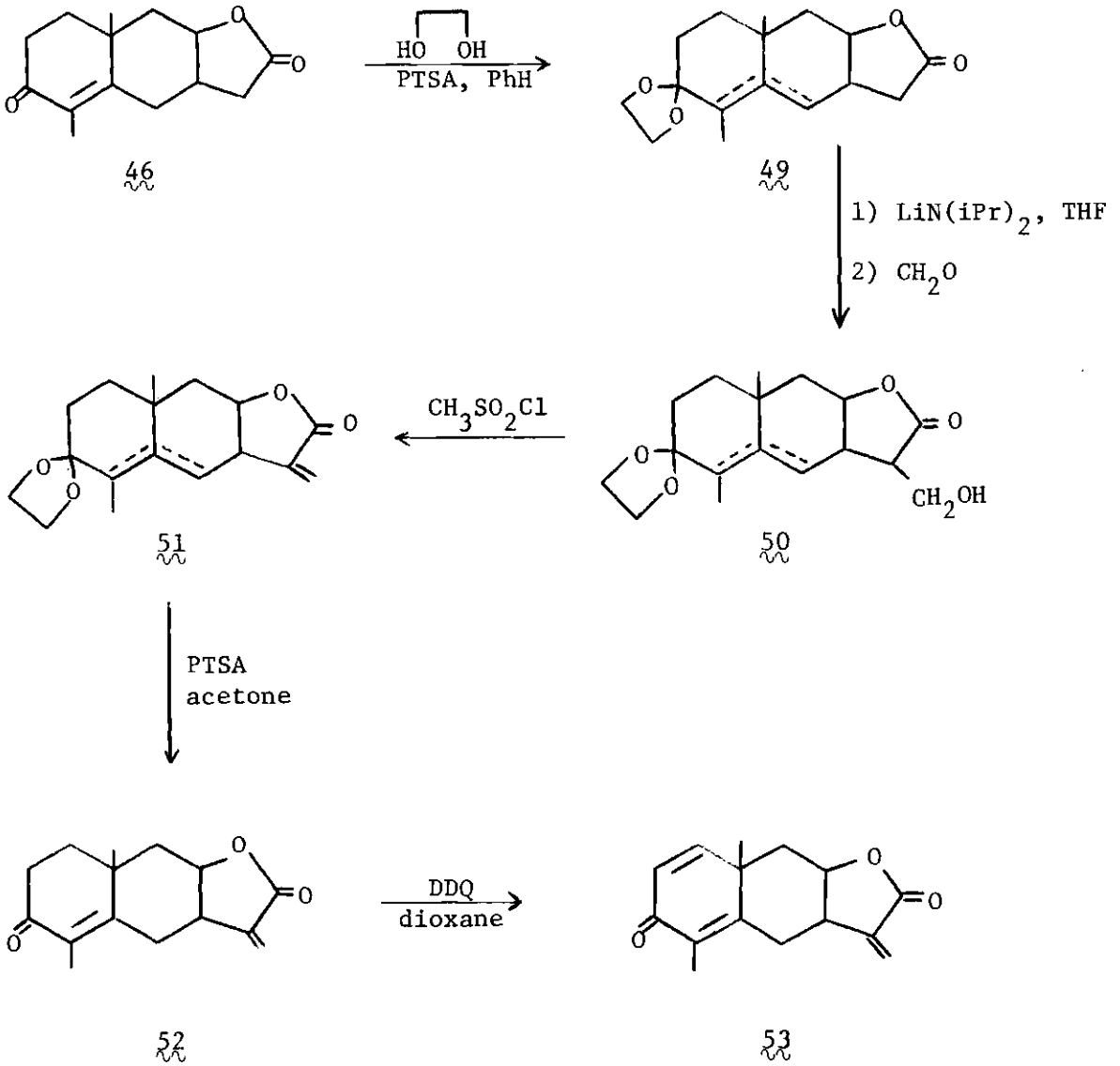
Composition by nmr	95	:	5
Isolated yield	54%		

Scheme 12

Potassium Selectride was found to give acceptable yields of lactone 46 and was the reagent of choice. Evidence supporting the structure of 46 was the lactone absorption in the infrared spectrum at 1775 cm^{-1} and the nmr signal at 4.63 (m, 1H) for the C-6 proton. Other spectral properties were largely unchanged from keto ester 45 except for

the slight change in position of the bridgehead methyl signal from δ 1.24 to 1.30.

In order to confirm stereochemical assignments and to test a method for subsequent introduction of an α-methylene group in the lactone ring, a synthesis of naturally occurring compound yomogin was projected as shown in Scheme 13.

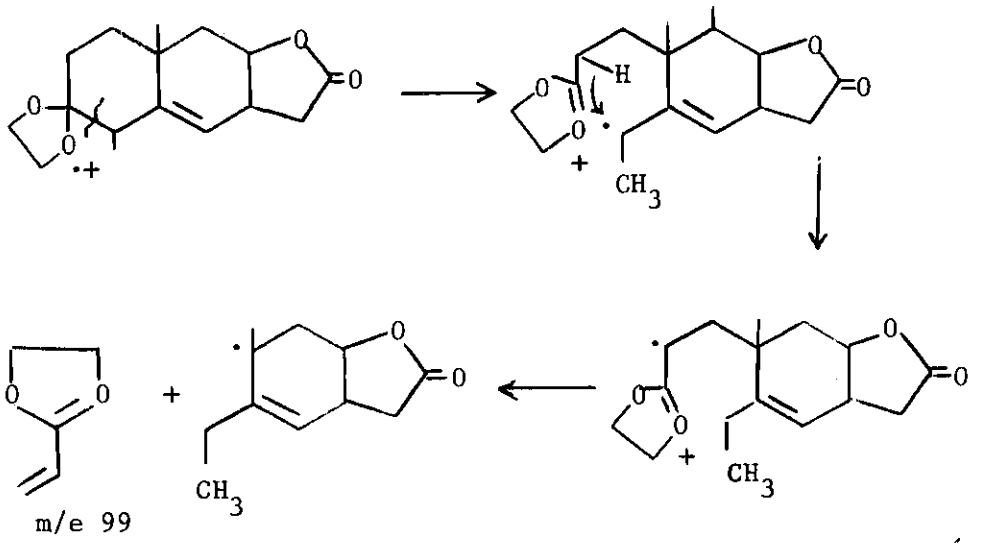


46 49 50 51 52 53

Scheme 13

Ketalization of 45 was difficult to perform under normal conditions and extensive decomposition was seen in the product. However, under conditions used by Ourisson,[23] good yields of ketal lactone 49 were obtained. The major difficulty with this reaction was that it could not be scaled up over a one gram level without significant decomposition of the product. Also, the ketal lactone was unstable in the workup procedure unless a small amount of pyridine was present. Due to this instability, it was decided not to attempt to isolate compounds having the ketal functionality in pure form.

Ketal lactone 49 appeared to be a 1:1 mixture of double bond isomers as evidenced by a vinyl proton signal at δ 5.13 which integrated for one half a hydrogen. Also, a very intense peak at m/e 99 was observed in the mass spectrum which could arise from the fragmentation pathway shown in Scheme 14. Fragmentations of this type are well known.[35]



Scheme 14.

Hydroxymethylation of 49 was carried out according to the procedure of Grieco and Hiroi.[24] Lithium diisopropylamide in THF at -78° formed the enolate anion of 49 which was reacted with gaseous formaldehyde to form the hydroxymethyl lactone 50. This product showed a peak at 3450 cm^{-1} in the infrared spectrum corresponding to the hydroxyl group. However, the corresponding signal in the nmr spectrum was apparently obscured by the signal for the ketal protons. No molecular ion was observed in the mass spectrum but a peak at m/e 290 (M-18) was observed.

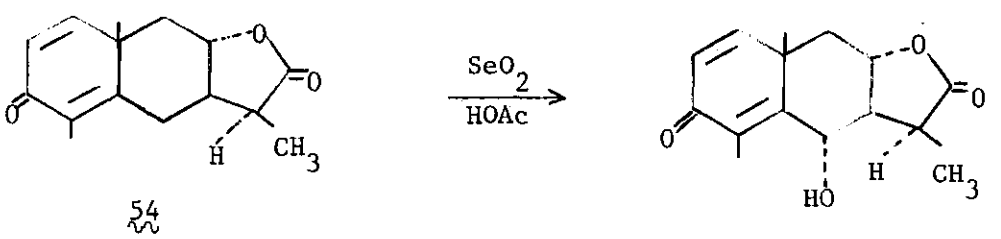
Dehydration of 50 with methanesulfonyl chloride was unremarkable and gave a 74% yield of α-methylene lactone 51. The lactone absorption in the infrared spectrum was shifted to longer wavelength (1761 cm^{-1}) consistent with an α-methylene lactone. Vinyl hydrogen absorptions at δ 6.14 and 5.61 ppm were also observed. A molecular ion peak at m/e 290 was seen but was too small for an accurate exact mass determination.

Transketalization of 51 with PTSA and acetone gave a 45% yield of dihydro-(±)-yomogin 52. In contrast to the ketal lactone intermediates, 52 was amenable to isolation in pure crystalline form and was fully characterized. Compound 52 exhibited infrared absorptions at 1764 and 1660 cm^{-1} consistent with the enone and lactone functionalities. Nmr absorptions at δ 1.25 (s, 3H, 10-CH_3), 1.83 (broad s, 3H, 1-CH_3), 4.64 (mult., 1H, 6-H), 5.78 (d, J = 2.8 Hz, 1H, =CH_2), and 6.40 (d, J = 2.8 Hz, 1H, =CH_2) were also consistent with the structural assignment. Exact mass determination and elemental analyses were in accord with the calculated values.

Oxidation of 52 with DDQ in dioxane proceeded in 62% yield to

give crystalline (±)-yomogin, m.p. 170-172°. Nmr, infrared, and mass spectra of the synthetic material were identical to the nmr, infrared, and mass spectra of the natural product.[25] This constitutes the first total synthesis of (±)-yomogin.

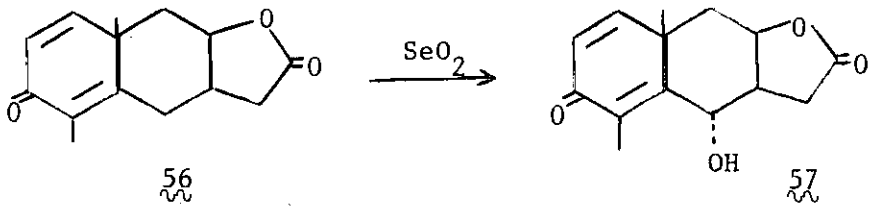
Having successfully attained the objectives of the yomogin synthesis, it was decided to pursue the problem of introducing the C-8 hydroxyl group into the molecule in a stereoselective fashion. Nakazaki and Naemura, in connection with their synthesis of artemisin, successfully converted 54 into 55 as shown in Scheme 15.[36]



54 55

Scheme 15.

Similarly, it was felt that dienone 56 should be readily convertible into the analogous C-8 hydroxy compound 57 as shown in Scheme 16.

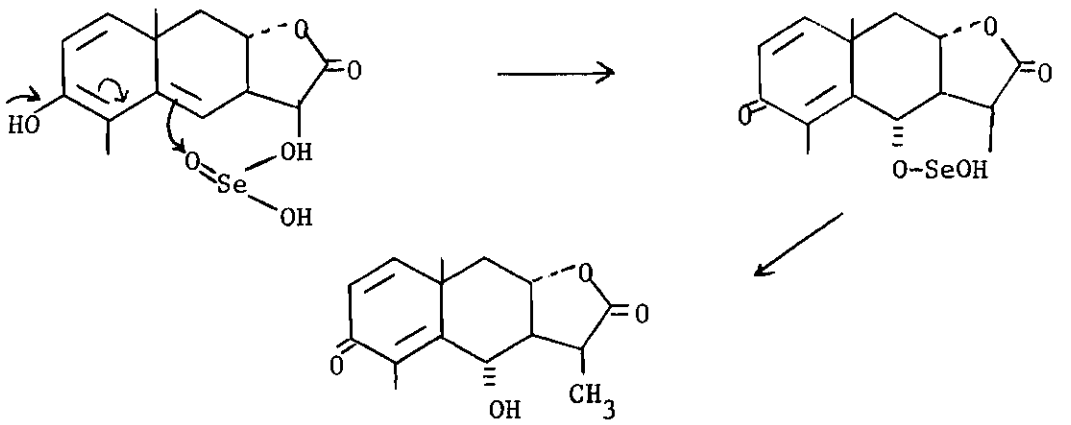


56 57

Scheme 16

Dienone lactone 56 was prepared in 35% yield by DDQ oxidation of enone lactone 46 in refluxing dioxane. Signals at δ 6.90 and 6.28 ppm in the nmr spectrum confirmed the presence of the cross conjugated dienone and distinct absorptions for the two double bonds were observed at 1628 and 1606 cm^{-1} in the infrared. Carbon and hydrogen analysis agreed with the calculated values.

Although the dienone lactone 56 is closely related to the isomeric dienone lactone 54, allylic hydroxylation of the former compound could not be carried out with selenium dioxide in several solvents including aqueous acetic acid, anhydrous dioxane, and tert-butyl alcohol containing a catalytic amount of acetic acid. In each case, the starting material was recovered unchanged at the end of the reaction. While the exact mechanism of the allylic hydroxylation of 54 is not known, a likely possibility is that the reaction involves attack of selenium dioxide or its hydrate upon the enol form of the dienone to produce the selenite ester intermediate which then is hydrolyzed to produce the hydroxy compound (Scheme 17).

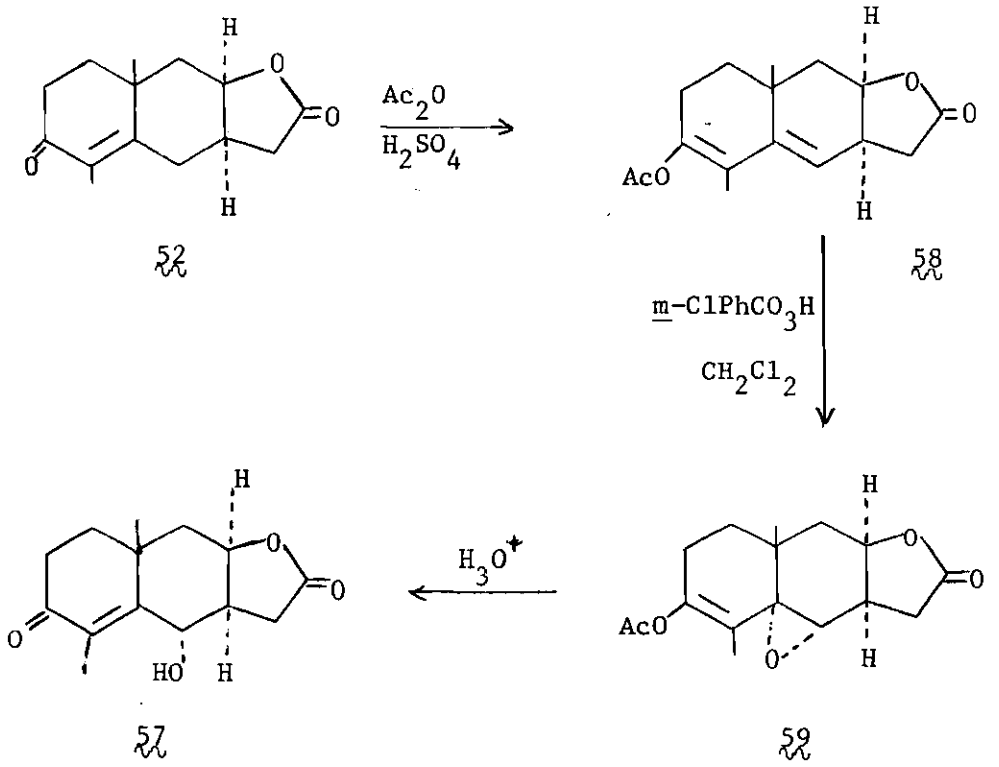


55

Scheme 17.

Examination of models of the enol form of 56 does not indicate that this species would be exceptionally strained. However, if ring B of the starting material is considered to remain in a chair conformation, the transition state for formation of the enol might be expected to be of rather high energy. This is because removal of the 8 β-proton (axial) by some weak base (probably water) would be hindered by a 1,3-diaxial interaction involving both the 10 β-methyl group and the 6 β-oxygen of the lactone ring. Thus it is possible that the rate of formation of the enol of 56 is much slower than the rate of formation of the enol of 54 and that for this reason the former is unreactive toward selenium dioxide.

Another approach to functionalizing the C-8 position was the preparation of enol acetate 58, epoxidation, and subsequent hydrolysis as shown in Scheme 18. An analogous procedure was reported by Abe in the synthesis of santonin.[26]



52 58 57 59

Scheme 18.

Enone lactone 52 was converted smoothly into the heteroannular dienol acetate 58 in 45% yield by treatment with acetic anhydride containing a trace of sulfuric acid. An infrared absorption at 1752 cm^{-1} for the enol acetate carbonyl group and a doublet (J = 2 Hz) for the C-8 vinylic proton in the nmr spectrum of the product were consistent with the structural assignment. Furthermore, an ultraviolet absorption maximum at 236 nm (ε 26,500) in 95% ethyl alcohol confirmed that the diene system was heteroannular rather than homoanular. Other spectral properties as well as an exact mass determination on the parent ion and a correct carbon-hydrogen elemental analysis agreed with the

structural assignment of 58.

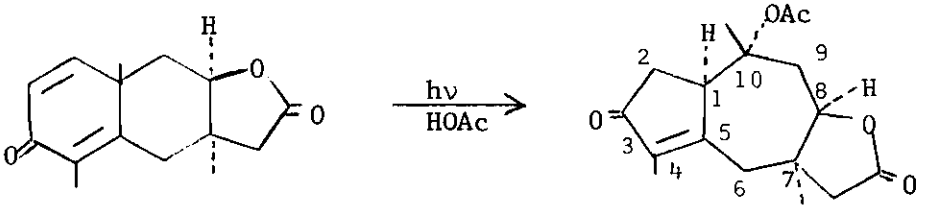
The results of the attempted epoxidation of 58 were variable. If m-chloroperbenzoic acid (85%, Eastman) was used directly without purification, no reaction occurred and the starting material could be recovered unchanged. However, if the peracid was purified according to the procedure of Schwartz and Blumbergs[37] by washing with pH 7.5 buffer, a crude product was obtained which did not show a vinyl hydrogen signal at δ 5.40 ppm in the nmr spectrum. The enol acetate functionality apparently remained intact as the infrared absorption band at 1752 cm^{-1} was retained. However, the crude product showed three spots on thin layer chromatography; two having Rf values of 0.71 and 0.22, and one remaining at the origin. Preparative tlc allowed isolation of the two more polar compounds which exhibited similar spectra to the crude material. Anomalous signals were observed in the aromatic region of the nmr spectrum for both the crude and the purified materials.

Hydrolysis of the crude product was attempted by treatment with oxalic acid in dioxane but the nmr and infrared spectra indicated that only starting material was recovered. Attempted hydrolysis with potassium hydroxide in aqueous methanol gave a crude product having a strong infrared absorption at 1720 cm^{-1} indicative of a saturated carbonyl compound. No absorption corresponding to a hydroxyl group or an α,β-unsaturated carbonyl group were observed. Attempted purification by column chromatography on silica gel led to irreversible absorption of the compound onto the silica gel. Since the spectra of the crude product did not correlate with the structure of the desired product, the reaction was not investigated further.

Another approach to introduction of oxygen functionality at C-8 of the enone lactone 52 involved reaction of the enol acetate 58 with lead tetraacetate. Kirk and Wiles[30b] have reported that the $\Delta^{3,5}$-3-acetoxy derivatives of Δ^{4}-3-keto steroids yield a 6α-acetoxy derivative on reaction with lead tetraacetate. A similar oxidation of 58 was attempted under the conditions described by Nambara and Fishman[30a] for oxidation of simple steroidal enol acetates. This involved reaction of 58 with one equivalent of lead tetraacetate in glacial acetic acid at room temperature overnight. However, on workup of the reaction mixture only the starting material was recovered. Under more drastic conditions (80°, 12 hr) a mixture which contained at least four components and showed no appreciable infrared absorptions characteristic of an α,β-unsaturated ketone grouping. This approach was not investigated further.

Since all attempts to introduce oxygen functionality at the 8-position of the diene lactone 56 failed, it was decided that if possible this compound should be converted into the corresponding 5/7 fused photoproduct which possibly would undergo the desired oxidation to yield an intermediate which would be useful for the synthesis of euparotin. Examination of the literature revealed that while Barton and coworkers and others[38] have carried out photochemical rearrangements of dienone lactones of the α-santonin type in which the γ-lactone ring is trans or cis fused at C-7 and C-8 of the B ring. No examples of rearrangements of systems having a γ-lactone fused at C-6 and C-7 of the B ring as in 56 had been reported. However, examination of models of the hypothetical mesoionic intermediate analogous to 13 (p. 4) derived from

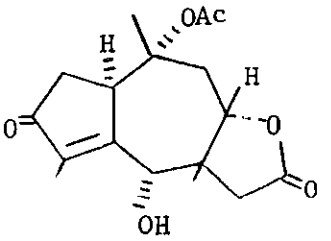
56 did not reveal any unusual strain or steric hindrance associated with the lactone ring and the photochemical rearrangement was expected to occur smoothly. This proved to be the case because irradiation of 56 in glacial acetic acid for 3 hr using Pyrex filtered irradiation from a Hanovia high pressure mercury lamp led to the isolation of a 50% yield of the 5/7-fused acetoxy ketone 60 (Scheme 19). The infrared spectrum of 60 showed carbonyl absorptions at 1771, 1721, and 1701 cm^{-1} for the lactone, acetate ester, and cyclopentenone carbonyl groups, respectively, and an absorption at 1640 cm^{-1} characteristic of a conjugated carbon-carbon double bond. The nmr spectrum of the photoproduct showed a multiplet at δ 5.26 for the 8 α-proton (see numbering system on structure 60), sharp singlets at δ 2.00 for the acetate methyl group and at δ 1.25 for the 10-methyl group, and a broad singlet at δ 1.70 for the 4-methyl group. A one proton multiplet at δ 3.60 and a two proton doublet at δ 2.45 was assigned to the 1-methine and 2-methylene protons respectively. Decoupling experiments verified the spin-spin coupling interaction of these groups of absorptions. Similar apparent AB_2 patterns have been observed for related acetoxy ketones.[39]



59 60

Scheme 19.

Attempted selenium dioxide oxidation of this compound in aqueous dioxane gave a crude product which exhibited at least five significant compounds on thin layer chromatography. Unfortunately, the infrared spectrum of the material did not reveal the presence of strong hydroxylic absorption which would indicate the presence of the desired hydroxy compound 61. Further investigation of this reaction mixture was not attempted.



61

CHAPTER V

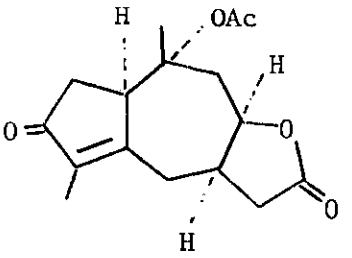
CONCLUSIONS

Although the primary objective of this research, the synthesis of a 5,7-fused intermediate 21 (R = H or CH_3) was not attained, several positive secondary objectives have been achieved. The enamine alkylation of diketone 32 has demonstrated that alkylations can be performed alpha to a normal carbonyl group in the presence of an α-substituted α,β-unsaturated ketone. This method may have utility in other syntheses requiring intermediates with fused lactone rings.

A total synthesis of (±)-yomogin from intermediate 45 has firmly established the stereochemistry of the lactone ring in this intermediate. Also, on its own merits, this is the first reported total synthesis of (±)-yomogin.

Several methods have been attempted to effect hydroxylation of the C-8 position in intermediate 45. The failure of these methods indicate that there may be some inherent difficulty in the synthesis of 1,3-dihydroxy compounds which have a side chain between them. This difficulty may be reflected in the scarcity of publications of syntheses of homoallylic hydroxy α-methylene lactones.[40]

The synthesis of the 5,7-fused intermediate 60 is a positive achievement inasmuch as four of the seven asymmetric centers present in euparotin have been introduced.



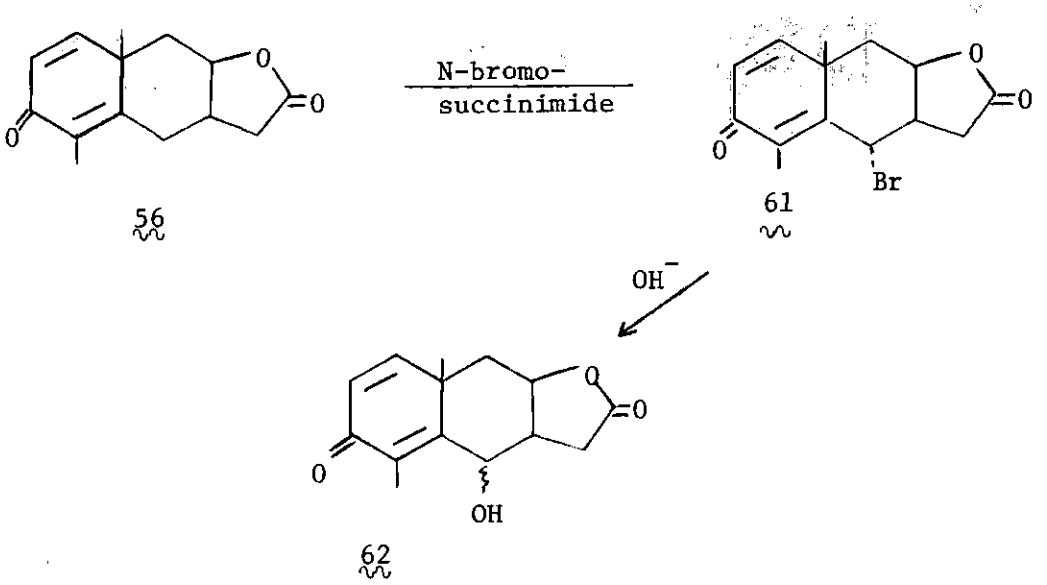
60

Also, intermediate 60 may be a convenient model compound for further study of synthetic approaches to euparotin (e.g. a model for the Wharton reaction).

CHAPTER VI

RECOMMENDATIONS

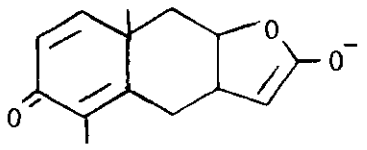
Since the primary objective of this research has not been attained, further exploration of a route to hydroxylation of compound 56 is warranted. One possibility would be a study of allylic bromination and subsequent displacement as shown in Scheme 20. However, if initial bromination takes place on the β side, an S_N2 displacement might be predicted to occur from the α face. The unknown factor is whether the bridgehead methyl group might block an S_N2 approach, facilitating an S_N1 type reaction or simple elimination.



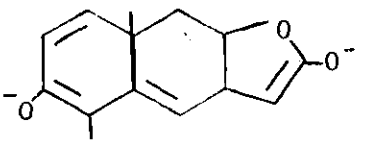
56 61 62

Scheme 20.

Another suggestion might be made with regard to the synthesis of (±)-yomogin. Since the ketalization and deketalization steps of the present synthesis are the most troublesome, a method may be proposed in which these steps are eliminated. An attempt could be made to prepare enolate anion 63 directly from 56 under kinetic conditions and hydroxymethylation could then be done selectively. If this approach is unsuccessful, dianion 64 might be prepared and subjected to hydroxymethylation. Reaction would be predicted to occur α to the lactone functionality due to steric constraints.



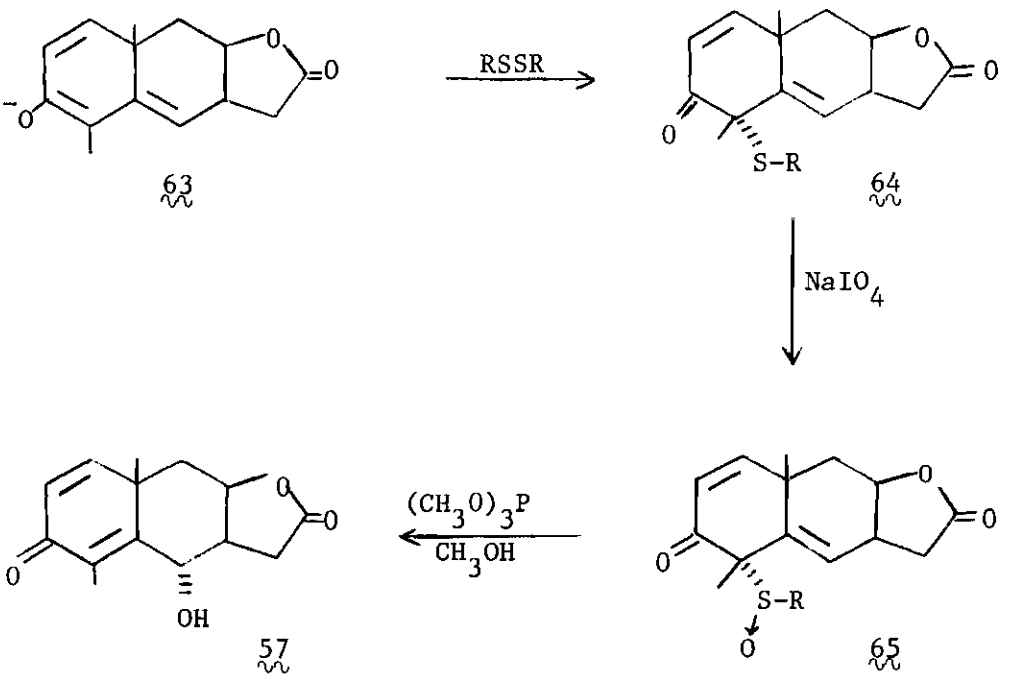
63



64

Since steric factors involved in the selenium dioxide hydroxylation are not clear, the reaction should be attempted on yomogin. In accord with Guillemonat's rules, the allylic methylene group should be more readily oxidized than the alternative methine position.

Another potential approach to the introduction of a hydroxyl group in the C-8 position arises from the work of Evans and Andrews[41] on the rearrangement of allylic sulfoxides. Dienone lactone 56 should be readily convertible to its thermodynamic enolate 63 (see Scheme 21).



Scheme 21.

Alkylation with a disulfide or a sulfur transfer reagent[42] should proceed from the less hindered α side to give the unsymmetrical sulfide 64. Oxidation to the sulfoxide followed by treatment with trimethylphosphite to force the (2,3) sigmatropic rearrangement to proceed to the desired C-8 hydroxy compound 57 should be attempted.

LITERATURE CITED

1. (a) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, J. Med. Chem., 14, 1147 (1971).

   (b) K. H. Lee, H. Furukawa, and E. S. Huang, J. Med. Chem., 15, 609 (1972).

   (c) K. H. Lee, R. Meek, C. Piantadosi, and E. S. Huang, J. Med. Chem., 16, 299 (1973).

   (d) G. A. Howie, P. E. Manni, and J. M. Cassady, J. Med. Chem., 17, 840 (1974).

   (e) A. Rosowsky, N. Papathanasopoulos, H. Lazarus, G. E. Foley, and E. J. Modest, J. Med. Chem., 17, 672 (1974).

2. P. A. Grieco, Seminar at Georgia Institute of Technology, October 18, 1974.

3. D. H. R. Barton, P. deMayo, and M. Shafig, J. Chem. Soc., 140 (1958).

4. (a) H. E. Zimmerman and D. I. Schuster, J. Am. Chem. Soc., 84, 4527 (1962).

   (b) H. E. Zimmerman and J. S. Swenton, J. Am. Chem. Soc., 89, 906 (1967).

5. D. H. R. Barton, J. T. Pinhey, and R. J. Wells, J. Chem. Soc. 2518 (1964).

6. E. Piers and K. F. Cheng, J. Chem. Soc. D, 562 (1969).

7. E. H. White, S. Eguchi, and J. N. Marx, Tetrahedron, 25, 2099 (1969).

8. D. Caine and P. F. Ingwalson, J. Org. Chem., 37, 3751 (1972).

9. D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, J. Chem. Soc., 3472 (1962).

10. P. S. Wharton, J. Org. Chem., 26, 4781 (1961).

11. H. B. Henbest, Proc. Chem. Soc., 159 (1963).

12. (a) E. E. vanTamelen and S. R. Bach, J. Am. Chem. Soc., 77, 4683 (1955) and 80, 3079 (1958).

12. (b) H. Minato and I. Horibe, Chem. Commun., 531 (1965).

(c) J. A. Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965).

(d) H. Minato and I. Horibe, J. Chem. Soc., 1575 (1967).

(e) E. S. Behare and R. B. Miller, Chem. Commun., 402 (1970).

(f) J. Martin, P. C. Watts, and F. Johnson, Chem. Commun., 27 (1970).

(g) J. W. Patterson and J. E. McMurray, Chem. Commun., 488 (1971).

(h) L . K. Dalton and B. C. Elmes, Aust. J. Chem., 25, 625 (1972).

(i) P. A. Grieco and K. Hiroi, Chem. Commun., 1317 (1972).

(j) A. E. Greene, J. C. Muller, and G. Ourisson, Tetrahedron Lett., 2489 (1972).

(k) A. E. Greene, J. C. Muller, and G. Ourisson, ibid., 3375 (1972).

(l) K. Yamada, M. Kato, M. Iyoda and Y. Hirata, Chem. Commun., 499 (1973).

(m) P. A. Grieco and K. Hiroi, Chem. Commun., 500 (1973).

(n) P. A. Grieco and K. Hiroi, Tetrahedron Lett., 1831 (1973).

(o) A. D. Harmon and C. R. Hutchinson, Tetrahedron Lett., 1293 (1973).

(p) R. C. Ronald, Tetrahedron Lett., 3831 (1973).

(q) K. Yamada, M. Kato, Y. Hirata, Tetrahedron Lett., 2745 (1973).

(r) P. F. Hudrilik, L. R. Rudnick, and S. H. Korzeniowski, J. Am. Chem. Soc., 95, 6848 (1973).

(s) J. L. Herrmann, M. H. Berger, and R. H. Schlesinger, J. Am. Chem. Soc., 95, 7923 (1973).

(t) For recent reviews see (a) P. A. Grieco, Synthesis, 67 (1975); (b) R. B. Gammill, C. A. Wilson, and T. A. Bryson, Synth. Commun., 5, 245 (1975).

13. S. A. Narang and P. C. Dutta, J. Chem. Soc., 2842 (1960).

14. S. Rajagopalan and P. V. A. Raman in "Organic Syntheses," W. E. Bachmann, Ed., John Wiley & Sons, Inc., New York, Vol. 25, 1955, p. 51.

15. W. S. Emerson and R. I. Longley in "Organic Syntheses," N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, Coll. Vol. IV, p. 302.

16. R. M. Lukes, G. I. Poos, and L. H. Sarett, J. Am. Chem. Soc., 74, 1401 (1952).

17. (a) Y. A. Arbuzov and Y. P. Vokov, J. Gen. Chem. USSR, 29, 3242 (1959).

(b) Alternatively, the crude chloroketone can be distilled at 54-56 (20 mm) and stored for the next step until the ethyl vinyl ketone is needed.

18. Conditions were those used by N. C. Ross and R. Levine, J. Org. Chem., 29, 2341 (1964).

19. C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 2680 (1960).

20. A. B. Turner and H. J. Ringold, J. Chem. Soc. C, 1720 (1967).

21. F. J. Agnello and G. D. Laubach, J. Am. Chem. Soc., 82, 4293 (1960).

22. Analogous systems are described in:

(a) M. Nakazaki and K. Naemura, Bull. Chem. Soc. Jap., 42, 3366 (1969); Tetrahedron Lett., 33 (1969).

(b) J. A. Marshall, N. Cohen, and A. R. Hochsteller, J. Am. Chem. Soc., 88, 3408 (1966).

23. (a) A. E. Greene, J. C. Muller, and G. Ourisson, Tetrahedron Lett., 4147 (1971).

(b) J. C. Muller, personal communication.

24. P. A. Grieco and K. Hiroi, Chem. Commun., 1317 (1972).

25. We are grateful to Professor T. A. Geissman of U.C.L.A. for providing a sample of yomogin. See T. A. Geissman, J. Org. Chem., 31, 2523 (1966).

26. Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, J. Am. Chem. Soc., 78, 1422 (1956).

27. A. Furlenmeier, A. Furst, A. Langemann, G. Waldvogel, J. Kerb, P. Hocks, and R. Wiechert, Helv. Chim. Acta., 49, 1591 (1966).

28. L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, Vol. 1, 1967, p. 135.

29. Ibid., p. 537.

30. (a) Reaction conditions are those used by T. Nambara and J. Fishman, J. Org. Chem., 27, 2131 (1962).

(b) D. N. Kirk and J. Wiles, unpublished work. See D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier Publishing Co., New York, 1968, p. 184.

31. J. F. DeBardeleben, Jr., Ph.D. Dissertation, Georgia Institute of Technology, 1967, pp. 88-89.

32. (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1969, pp. 242-244.

(b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, pp. 14-24.

33. C. Djerassi and J. Gutzwiller, J. Am. Chem. Soc., 88, 4537 (1966).

34. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Am. Chem. Soc., 85, 207 (1963).

35. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, Inc., 1964, pp. 26-28.

36. M. Nakazaki and K. Naemura, Tetrahedron Lett., 2615 (1966).

37. N. N. Schwartz and J. H. Blumbergs, J. Org. Chem., 29, 1976 (1964).

38. For reviews on dienone photochemistry see: (a) P. J. Kropp, Org. Photo. Chem., 1, 1 (1967); K. Schaffner, Adv. Photo. Chem., 4, 81 (1966).

39. See D. Caine and F. N. Tuller, J. Org. Chem., 38, 3663 (1973).

40. (a) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Stadt, Tetrahedron Lett., 2035 (1974).

(b) P. A. Grieco and K. Hiroi, Tetrahedron Lett., 3467 (1974).

41. D. A. Evans and G. C. Andrews, Accts. Chem. Res., 7, 147 (1974).

42. P. T. S. Lau, Eastman Organic Chemical Bulletin, 46, No. 2, 1975.

VITA

Gerard L. Hasenhuettl was born in Erie, Pennsylvania on February 22, 1944 and is the son of Frank and Marie Hasenhuettl. He attended St. Mary's Elementary School and graduated from Cathedral Preparatory School in 1962. He then attended Gannon College where he graduated in 1966 with a Bachelor of Arts in Chemistry. After a short period of employment with Mallinckrodt Chemical Company he received his Master of Science degree in 1969 from Niagara University. Later that same year the author entered the doctoral program at Georgia Institute of Technology.

The author is married to the former Julia Ann Kopas of Erie, Pennsylvania and they have one daughter. He is presently a Postdoctoral Research Associate at Fels Research Institute of Temple University.